Medical and oncological management of malignant mesothelioma

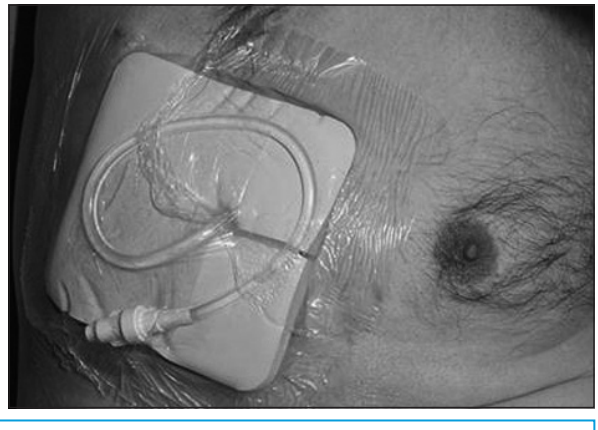
Mesothelioma is an aggressive cancer, for which no curative oncological treatment currently exists. This article outlines the options for managing malignant pleural effusions, describes the developments in chemotherapy over the past 10 years and summarizes the evidence for prophylactic and palliative radiotherapy.

Mesothelioma is a malignant disease of serous membranes, which affects the pleural surface in over 80% of cases. The majority of patients present with disease that cannot be surgically resected, and is therefore incurable. Management focusses on reducing symptoms, preventing disease spread and prolonging life expectancy. This article outlines the medical and oncological options for managing malignant mesothelioma, including control of pleural effusions, radiotherapy and chemotherapy.

Control of pleural effusions

Patients with pleural effusions who derive symptomatic benefit from fluid removal should undergo a definitive procedure to prevent fluid re-accumulation. Options for controlling pleural fluid include chest tube drainage with talc pleurodesis, insertion of an indwelling pleural catheter (*Figure 1*) or thoracoscopy with talc poudrage (*Figure 2*). Frail patients with very limited life expectancy may be suitable for recurrent therapeutic aspirations, but they are a minority, and a definitive procedure should be the goal for most. The benefits and risks of the different procedures are described below, and summarized in *Table 1*.

Figure 1. An indwelling pleural catheter.



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Indwelling pleural catheters *vs* chest drains with talc pleurodesis

In the TIME 2 trial, Davies et al (2012) showed that both indwelling pleural catheters and chest tube drainage with talc pleurodesis are effective at relieving breathlessness and chest pain in patients with malignant pleural effusions, with no significant differences between the two methods. Because they are usually inserted as a day-case procedure, indwelling pleural catheters were associated with shorter hospital stays compared with pleurodesis via a chest drain which required an average inpatient stay of 4 days. Indwelling pleural catheters were associated with higher rates of pleural infection, although in the largest prospective series of patients with indwelling pleural catheters to date, Fysh et al (2013) reported infection rates of less than 5%, of whom 40% were successfully managed with oral antibiotics.

Thoracoscopy and talc poudrage

Thoracoscopy with talc poudrage is another method of achieving fluid control. Thoracoscopy can be a surgical

Figure 2. Talc poudrage, visualized via thoracoscopy. A fine layer of talc can be seen covering the visceral pleura at the bottom of the image, with signs of recent biopsies of the parietal pleura seen in the upper left of the image.

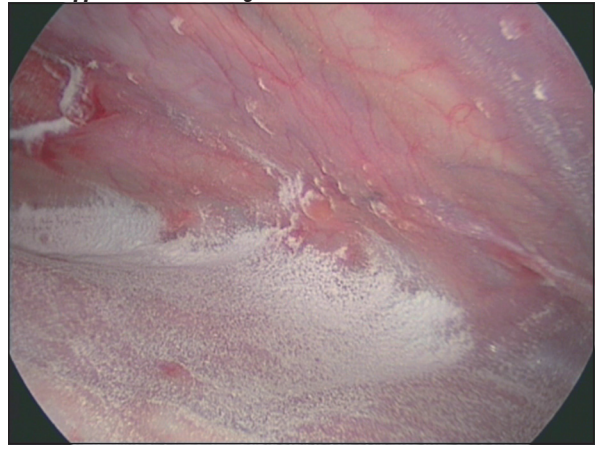
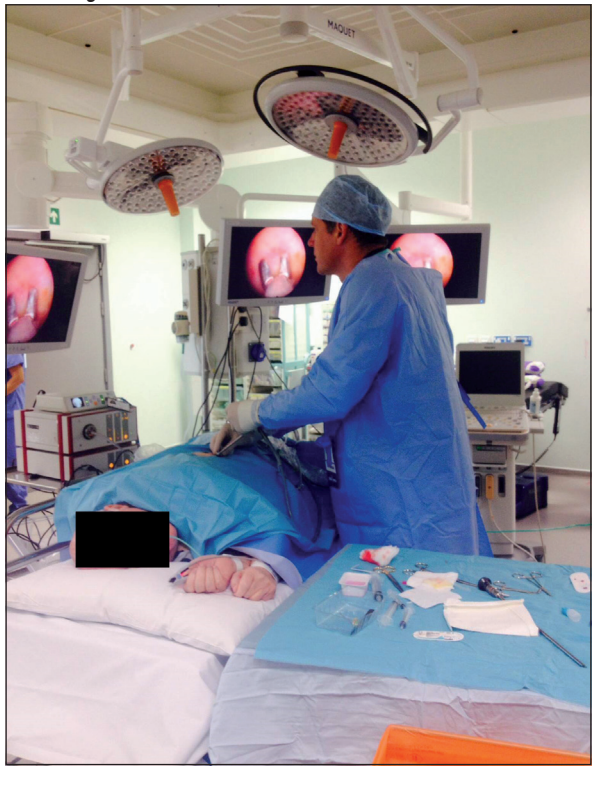


Table 1. Advantages and disadvantages of methods of controlling pleural effusions

	Advantages	Disadvantages
Intercostal chest drain with talc pleurodesis	Definitive procedure	Pain
	75% successful pleurodesis rates	Inpatient stay (average 4 days)
	Patient discharged with no visible reminder of disease	Failure rate (22% required further intervention in Davies et al's (2012) study)
Insertion of indwelling pleural catheter	Day case procedure with home drainage	Some patients may not want permanent reminder of disease
	Effective for patients with trapped lung	Risk of infection ~5%
	Empowers patients and improves quality of life	Need to coordinate insertion with timing of chemotherapy to minimize infection risk
	Spontaneous pleurodesis in ~60%	Risk of tumour seeding
		Community nurses (or patients) need training to regularly drain pleural fluid
Thoracoscopy with talc poudrage	Single procedure allowing diagnosis, drainage and pleurodesis	Limited to patients with good performance status
	1–2 day inpatient stay	Not universally accessible
	Poudrage marginally more effective than talc pleurodesis	Some patients may not wish to undergo invasive procedure
	Accessibility likely to improve in the future	Risk of tumour seeding – may need prophylactic radiotherapy following procedure

procedure, performed under general anaesthetic, or a medical intervention using local anaesthetic and sedation (*Figure 3*). This procedure promotes pleurodesis by distributing an even layer of talc across the pleural space, once fluid has been removed and pleural biopsies acquired (*Figure 2*). For some patients a single procedure with both diagnostic and therapeutic benefits is attractive, but others may be deterred by the invasive nature of the procedure, and a minority of people may not be suitable from the outset. There is weak evidence that talc poudrage may be slightly more effective than pleurodesis via a chest drain, but this will not be known for certain until the results of the multicentre, randomized TAPPS trial are available.

Figure 3. Local anaesthetic thoracoscopy. Pleural biopsies can be seen being taken on the screens.



Fluid management is equally important for patients with ascites secondary to peritoneal mesothelioma, although there is no equivalent of pleurodesis for the abdominal cavity. Recurrent paracentesis or ascitic drainage is often the only option. In-dwelling catheters have been used for ascites, but have a higher rate of complications as a result of the large volume of fluid drained and the risk of sepsis (Lee et al, 2000).

The ultimate decision about which fluid management method is optimal depends on a number of factors, including the patient's prognosis, overall fitness and individual preference. Each method has advantages and disadvantages (*Table 1*) and best practice will involve an open conversation between the physician, oncologist, specialist nurse and patient to determine which option is best.

Chemotherapy

For the 85–90% of people who present with unresectable disease, chemotherapy may be considered. However, chemotherapy is always palliative with benefits limited to patients with a good performance status. At present just one regimen, cisplatin and pemetrexed, is approved by the National Institute for Health and Clinical Excellence (2008), for use in patients with performance status 0-1 and advanced disease.

Historical treatment options

Before pemetrexed was licensed, chemotherapy for mesothelioma was based on evidence from early phase trials, many of which were underpowered. Response rates were universally less than 50% and no regimen successfully extended survival beyond 10 months (Fennell et al,

2008). In one phase 3 trial, Muers et al (2008) investigated whether the addition of chemotherapy, in the form of mitomycin, vinblastine and cisplatin or vinorelbine, to active symptom control enhanced survival and quality of life compared with active symptom control alone. They failed to demonstrate a survival benefit from adding chemotherapy to active symptom control alone, although exploratory sub-group analysis suggested the addition of vinorelbine may be beneficial. In their systematic review, Berghmans et al (2002) demonstrated that cisplatin was the most efficacious single agent, and cisplatin and doxorubicin had the best overall response rate for combination therapy. Treatment with two agents was more effective than with a single agent, but adding a third drug had no additional effect.

Antifolate agents

Gemcitabine was the first antifolate agent used in mesothelioma. As a single agent its therapeutic efficacy was limited, but in combination with cisplatin it demonstrated a modest effect, with response rates between 12% and 48% (Kelly et al, 2011). Before 2008, combination gemcitabine and cisplatin treatment was frequently used as first-line therapy in patients with mesothelioma.

Between 2003 and 2005, two landmark trials of new antifolate agents were reported, which changed the landscape of chemotherapy in mesothelioma (Vogelzang et al, 2003; van Meerbeeck et al, 2005). The agents, pemetrexed and raltitrexed, exert their effect by inhibiting key intracellular enzymes required for the synthesis of purines and pyrimidines, thus preventing DNA replication and tumour growth. These agents appear to be concentrated in mesothelioma cells, thus enhancing their clinical effect.

The first trial, by Vogelzang et al (2003), randomized 448 patients to pemetrexed and cisplatin or cisplatin alone. Participants had good performance status (Karnofsky score >70), predicted life expectancy of greater than 12 weeks and had not previously received chemotherapy. The study demonstrated a clinically and statistically significant difference in survival between the groups. Median survival in the pemetrexed plus cisplatin group was 12.2 months, compared with 9.3 months in the cisplatin group (P=0.02). Pemetrexed combination therapy appeared superior for many secondary outcomes, including overall response rate (41.3% *vs* 16.7%, P<0.0001), 1-year survival (50.3% *vs* 38.0%, P=0.012) and median time to progression (5.3 months *vs* 3.9 months, P=0.001). Three treatment-related deaths occurred in the first 43 patients treated with pemetrexed, thought to be a result of folate and vitamin B_{12} depletion. Consequently the study protocol was altered to include folic acid and vitamin B_{12} supplementation, and no further treatment-related deaths occurred. On the basis of this study, the National Institute for Health and Clinical Excellence (2008) recommended pemetrexed and cisplatin for use in the UK as first-line chemotherapy for mesothelioma.

Data from the US Expanded Access Programme suggested that there was little difference between cisplatin and carboplatin when used in combination with pemetrexed (Santoro et al, 2008). This open-label, non-randomized study of 1704 chemo-naive patients demonstrated similar overall response rates, median time to progression and 1-year survival rates in the two treatment arms. Thus while pemetrexed and cisplatin remains the regimen of choice, carboplatin is considered an acceptable alternative if cisplatin is contraindicated.

van Meerbeeck et al (2005) used raltitrexed in their European Organisation for Research and Treatment of Cancer (EORTC) phase 3 trial, where 250 patients were randomized to raltitrexed plus cisplatin or cisplatin alone. Median survival in the combination arm was 11.4 months compared with 8.8 months in the cisplatin arm. Objective response rates were higher in patients treated with raltitrexed (24% *vs* 14%). There were twice as many adverse events in the raltitrexed arm, predominantly neutropenia and nausea, but no treatment-related deaths.

Raltitrexed does not have a European licence for the treatment of mesothelioma, so pemetrexed and platinum have become established as first-line chemotherapy of choice for mesothelioma. The strict inclusion criteria of Vogelzang et al's study mean that the efficacy of pemetrexed is unknown in patients with poor performance status and there is frequently a reluctance to consider platinum-based combination therapy in older patients. Further research is required to study the specific effects of pemetrexed in these sub-groups. *Table 2* gives a summary of outstanding research questions in mesothelioma.

Timing of chemotherapy

No study has examined whether immediate treatment is more effective than deferring treatment until symptoms progress. In a small randomized trial of mitomycin, vinblastine and cisplatin, patients who received immediate treatment had a longer time to symptomatic progression and longer survival, although these results did not achieve significance (O'Brien et al, 2006). The risk that a patient's performance status may deteriorate and render the patient ineligible for treatment means that most oncologists advocate early chemotherapy. Further research is needed to determine whether this approach is optimum (*Table 2*).

Maintenance and second-line therapy

Pemetrexed and cisplatin are administered for 4–6 treatment cycles, depending upon response and toxicity. At present there is no evidence for maintenance treatment after initial first-line chemotherapy, but the ongoing CALGB 30901 trial is expected to provide further data on this. Similarly the value of re-challenging patients with pemetrexed and/or platinum when disease progresses is not known. Jassem et al (2008) demonstrated superior response rates and longer time to pro-

gression in patients re-treated with pemetrexed compared with patients randomized to best supportive care, but failed to show a difference in overall survival between the groups.

Consequently there is no consensus on second-line treatment for mesothelioma. Some clinicians advocate gemcitabine with a platinum-based agent, although there is no robust evidence supporting this combination. Gemcitabine with vinorelbine has shown moderate activity in previously-treated patients with relapsed disease, as has vinorelbine alone (Kelly et al, 2011). However, these studies were small and lacked control arms. Prospective, randomized controlled trials are needed to investigate potential second-line therapies in this under-researched area (*Table 2*).

Radiotherapy

Radiotherapy is used in mesothelioma to achieve local disease control and prevent recurrence at the primary site. It is used in three main contexts:

1. In the adjuvant setting after definitive surgical treatment
2. As prophylaxis after intercostal procedures
3. As palliation, i.e. for pain relief.

With radiotherapy there is a delicate balance between administering effective doses and preventing radiation-induced toxicity to the lung and surrounding tissues. Potential side effects of high-dose radiotherapy include nausea, fatigue, skin irritation, pneumonitis and mucositis.

Adjuvant radiotherapy

Patients who have resectable mesothelioma are usually managed with tri-modality treatment: maximal resection surgery, followed by adjuvant chemotherapy and radiotherapy. This approach has not been tested in randomized trials, and a Cochrane review was inconclusive as a result of the lack of rigorous studies (Chapman et al, 2006). However, it is generally accepted that survival can be improved by using tri-modality treatment in carefully selected patients. Two radiotherapy techniques are used in the postoperative setting, high-dose hemi-thoracic radiotherapy and intensity-modulated radiotherapy.

High-dose hemi-thoracic radiotherapy

Hemi-thoracic radiotherapy involves an external beam, delivered anterior-posterior to the hemi-thorax, including the mediastinum and original site of disease (see *Figure 4* for an example of the equipment used). This avoids irradiating the contralateral lung, but may include other vulnerable tissue, such as the heart and spinal cord, in the radiation field. The low tolerance of these tissues to radiation can limit the dose, causing under-dosing of adjacent areas of disease. Concerns about local recurrence rates and cardiopulmonary toxicity has led to this technique being largely replaced by intensity-modulated radiotherapy.

Table 2. Outstanding research questions in mesothelioma

Is thoracoscopic poudrage more effective at pleurodesis than chest drains with talc slurry? (TAPPS trial currently underway)
What is the most effective and least toxic method of delivering adjuvant radiotherapy, intensity-modulated radiotherapy or high-dose hemi-thoracic radiation?
Is trimodality treatment more effective than radiotherapy alone or postoperative radiotherapy?
Is there a role for chemo-radiotherapy?
Is palliative radiotherapy effective at reducing pain?
Is single-dose palliative radiotherapy as effective as multiple fractions?
How effective is prophylactic radiotherapy at reducing tract metastases? (SMART trial currently underway)
Can pemetrexed and cisplatin be used safely and effectively in older patients and patients with poor performance status?
Is immediate chemotherapy more effective than deferred treatment?
Is there a role for maintenance treatment? (CALGB 30901 trial currently underway with maintenance pemetrexed)
What second-line agents should be used to treat relapsed disease?
Which novel drugs and targeted therapies will be effective in mesothelioma?

Intensity-modulated radiotherapy

Intensity-modulated radiotherapy is a highly specific method of administering radiotherapy that enables precise delivery of radiation volumes and fields. It allows conformational mapping of tumour shapes in three dimensions and therefore minimizes toxicity to nearby tissues. However, the risk of ipsilateral radiation pneumonitis is still present. Rosenweig et al (2012) treated 36 patients with intensity-modulated radiotherapy, 56% of whom had undergone pleurectomy/decortication beforehand. Median survival was 26 months for surgery with radiotherapy and 17 months

Figure 4. A linear accelerator machine (to deliver external beam radiotherapy).

for radiotherapy alone, and 1- and 2-year survival was 75% and 53% respectively for those who underwent surgery and 69% and 28% in patients who did not. However, 20% of patients experienced grade 3 pneumonitis, with one death attributable to this. Minatel et al (2013) reported long-term follow up of 20 patients treated with pleurectomy/decortication and intensity-modulated radiotherapy. Median overall survival was 33 months, with 2- and 3-year survival 70% and 49% respectively, and 17% of patients experienced grade 2 or 3 pneumonitis.

The balance of benefit to risk is difficult, and selecting the right patients for radiotherapy is important. Well-designed randomized trials comparing radiotherapy alone, adjuvant radiotherapy and trimodality treatment are needed (*Table 2*).

Palliative radiotherapy

Palliative radiotherapy aims to relieve pain in patients with mesothelioma. It can be given as a single treatment to a painful area or over several fractions for a higher total dose. As with adjuvant radiotherapy, the balance between benefit and toxicity must be carefully considered. A systematic review of eight articles using palliative radiotherapy in mesothelioma found improvements in pain ranging from 0% to 69% of patients (Macleod et al, 2013). Consequently there is not enough evidence to support radiotherapy for pain control, although it is recommended by the British Thoracic Society and the European Society of Thoracic Surgeons (British Thoracic Society Standards of Care Committee, 2007).

Prophylactic radiotherapy

Mesothelioma is locally invasive and has the potential to seed along the tracts of previous interventions leading to subcutaneous metastatic deposits. The incidence of malignant seeding at procedure sites is approximately 19% (Boutin et al, 1995), with large bore procedures carrying a greater risk (Bydder et al, 2004). Prevention is desirable as metastases may cause significant symptoms and be refractory to radiotherapy or analgesia. However, trial data are contradictory as to the effectiveness of prophylactic radiotherapy. Boutin et al (1995) randomized 40 patients who had undergone chest wall procedures to radiotherapy or placebo. None of the 20 patients treated with radiotherapy developed subcutaneous metastases compared with 40% in the placebo arm ($P<0.001$). In direct contrast to these findings, O'Rourke et al (2007) found no difference in the incidence of tract seeding in 56 patients randomized to prophylactic radiotherapy or best supportive care. Bydder et al (2004) compared a single fraction of prophylactic radiotherapy with control in 43 patients following 58 procedures. There was no significant difference between the two arms, with tract recurrence of 10% in controls and 7% in the radiotherapy arm.

Interpretation of these trials is difficult as a result of small participant numbers. Additionally the radiation dose differed between trials. The incidence of tract metastases was lower in both control groups than previously quoted in the literature. The SMART trial, a randomized multi-centre study, is currently underway, comparing immediate radiotherapy with radiotherapy deferred until metastases develop. The Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma (PIT) study is also recruiting. This is a randomized phase III trial looking at radiotherapy *vs* no intervention following invasive pleural procedures. Results of both trials are awaited. Until this evidence is available, the British Thoracic Society advises that patients with good performance status should be offered radiotherapy to biopsy tracts. Patients who have minimally invasive procedures may not require radiotherapy.

Novel agents and immunotherapy

Agents targeting epidermal growth factor receptor, vascular endothelial growth factor and platelet-derived growth factor have been successful in treating other malignancies, including non-small cell lung cancer. Given that mesothelioma proliferation involves many of these factors, there was hope that these agents would offer new promise in mesothelioma. Unfortunately, despite demonstrating efficacy in pre-clinical studies, no targeted agent has shown convincing results in clinical trials. This may be because mesothelioma progression occurs through multiple mechanisms, and inhibition of one pathway is overcome by enhanced growth via other pathways. Nonetheless, as summarized by Olevsky et al (2014), more than 50 novel agents have undergone evaluation early phase trials to date, with phase 3 studies underway in the most promising.

Immunotherapy is another area of development in mesothelioma. Mesothelioma inhibits lymphocytes in the pleural space, thus reducing anti-tumour activity and enhancing local disease progression. The ability to overcome this immunosuppression is associated with enhanced survival. The goal of immunotherapy is to stimulate T cells in the pleura to act against tumour. Current agents under investigation include a recombinant immunotoxin targeted to cell surface proteins on mesothelioma cells, a listeria vaccine and a monoclonal antibody which blocks T cell inhibition (see Kindler (2008) and Olevsky et al (2014) for details). Pre-clinical work and early trials appear promising, and results from larger trials are awaited.

Conclusions

Mesothelioma is an aggressive malignancy, with no current curative medical treatment. However, mesothelioma management options have increased over the past decade and further developments are anticipated. To manage pleural effusions, patients can now choose between chest tube with talc pleurodesis, indwelling pleural catheters or

medical thoracoscopy with talc poudrage. Radiotherapy is available as an adjuvant to surgery in the context of trimodal treatment, or for pain relief and prevention of tract metastases. Currently pemetrexed and cisplatin is the only chemotherapy regimen recommended by NICE, but the field is expanding rapidly with multiple novel agents under investigation. Immunotherapy offers an exciting new treatment modality that may be appropriate for patients not suitable for conventional chemotherapy. Overall, the future of mesothelioma treatment looks hopeful, with translational research likely to have a significant impact on life expectancy and disease survival over the next 5–10 years. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The medical and oncological management of mesothelioma is always palliative, aimed at prolonging life and reducing symptoms.
- In-dwelling pleural catheters, thoracoscopic talc poudrage and chest drains with talc slurry are all effective ways of controlling pleural effusions.
- Adjuvant radiotherapy can be used in the minority of patients suitable for surgical resection.
- Palliative radiotherapy may reduce pain from mesothelioma.
- Prophylactic radiotherapy to the site of wide bore interventions should be offered to patients.
- Pemetrexed and cisplatin is the only palliative chemotherapy regimen licenced for use in the UK.
- Pemetrexed and cisplatin offers a median survival benefit of 2–3 months.
- There are numerous unanswered research questions in mesothelioma, and multiple trials of new drugs underway.