

## Systematic review

# The role of radical radiotherapy in the management of malignant pleural mesothelioma: A systematic review



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## ABSTRACT

Malignant pleural mesothelioma (MPM) is a devastating disease with limited treatment options and a dismal prognosis. Attempts to employ radical radiotherapy in this disease have been limited by the complex shape of the pleura and the dose restrictions necessitated by the close proximity of radiosensitive structures. Recent shifts towards a 'lung sparing' surgical approach in MPM have further heightened these challenges. The aim of this systematic review is to assess recent advances in radiotherapy planning and delivery, to ascertain how these developments have impacted on the feasibility of delivering photon-based, high-dose radiotherapy with radical intent in MPM. Three electronic databases were searched and a total of 249 articles reviewed. The challenge of generating high quality, practice-defining data for diseases such as MPM was highlighted by the identification of just two randomised studies. Much of the literature consisted of low quality, retrospective data with small cohorts and inconsistent reporting on radiotherapy techniques and dosimetry. Nevertheless, a number of prospective phase II studies were identified to suggest that radical doses of radiotherapy can be delivered safely after a lung sparing procedure in MPM, reporting encouraging survival data and acceptable levels of toxicity.

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Malignant pleural mesothelioma (MPM) is an aggressive and refractory disease with a prognosis of 6–8 months without treatment. It is a rare cancer which is insidious in its early stages and does not lend itself to accurate radiological interpretation for either staging or response assessment. The long latency period and its association with asbestos exposure means that this disease is most frequently seen in a cohort of older patients with additional co-morbidities, thereby making aggressive treatments more challenging to deliver. MPM has proved resistant to a number of therapeutic strategies and the absence of robust, randomised studies in this area has resulted in a lack of consensus on the 'optimal' radical treatment strategy.

The intention of this systematic review is to assess the role of radical radiotherapy in this disease. The use of radiotherapy in MPM has traditionally fallen into 3 categories: to reduce the risk of local metastasis at intervention sites; for palliation of pain; and as part of a tri-modality approach with curative intent in conjunction with surgery and chemotherapy. The use of radiotherapy in a prophylactic capacity is now falling out of favour following a number of negative trials, including a recently published randomised study of 203 patients [1–3]. Robust evidence supporting

the use of palliative radiotherapy in MPM was seen in a prospective phase II study, where a standard dose of 20 Gy given over 5 fractions was seen to have a clinically significant effect on pain in one third of patients [4].

The most aggressive therapy offered to patients with MPM is the trimodality approach of chemotherapy, surgery and radiotherapy. The rationale for radiotherapy in this setting is to 'sterilise' the post-operative volume in an attempt to prevent recurrent local disease. However, the complex shape of the pleura and the dose restrictions necessitated by the close proximity of neighbouring radiosensitive structures renders the safe delivery of high dose radiotherapy in this setting very challenging. Traditional radiotherapy delivery techniques have been found to be unfeasible, with high rates of toxicity and low rates of local control. Nevertheless, recent developments in radiotherapy planning and delivery have revolutionised our ability to dose escalate treatment to the post-operative clinical target volume, while keeping doses to normal tissues at an acceptable level.

These developments have come at a time when the surgical landscape of this disease is also changing. The traditional approach of extrapleural pneumonectomy (EPP) is an aggressive and technically difficult operation which aims to remove all macroscopic disease, including the underlying lung. Significant post-operative morbidity has been reported for this technique, even in experienced centres [5–7], but the first and only randomised trial to

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assess EPP was the Mesothelioma and Radical Surgery (MARS) feasibility study of 50 patients, which concluded that a larger study would not be viable because of the high mortality associated with the procedure [8]. This outcome prompted significant debate and disagreement, since this feasibility study was neither designed nor powered to assess the outcome of surgery versus no surgery. Nevertheless, EPP has now largely fallen out of favour, and the option of pleurectomy/decortication (PD) has become more popular for patients with operable disease. Data from a multicentre non-randomised study of 663 patients suggest that this less radical approach, which leaves the underlying lung intact, is associated not only with lower rates of intraoperative mortality (7% for EPP compared to 4% for PD), but also with a survival benefit (median overall survival of 12 months for EPP compared to 16 months for PD,  $p < 0.001$ ) [9]. More recently, a survival meta-analysis of 2903 patients concluded that EPP was associated with significantly higher short-term mortality rates than PD (percent mortality meta estimate: 4.5% vs 1.7%;  $p < 0.05$ ) [10]. The shift away from EPP towards PD has presented a further challenge for the radiation oncologist in that the post-surgical delivery of high dose radiotherapy to the hemithorax now needs to be achieved in the context of two intact, radiosensitive lungs.

The aim of this report is to review the recent advances which have taken place in radiotherapy planning and delivery techniques, and to ascertain how these developments have impacted on the feasibility of using photon-based high-dose radiotherapy with radical intent in mesothelioma.

## Methods and results

Relevant articles were found by searching three electronic databases: Embase, MEDLINE (1946 to present) and PubMed. The search terms 'mesothelioma' and 'radiotherapy' were used in full and truncated formats, and no limits were applied. Relevant articles were also identified through hand-searching. An overview of the search is shown in Fig. 1. A more detailed description of the literature search, including details of articles which were subsequently excluded from the review, is given in Appendix 1.

A total of 249 articles were reviewed in detail. The nature of these articles is shown in Table 1.

**Table 1**  
Categorisation of articles reviewed in detail.

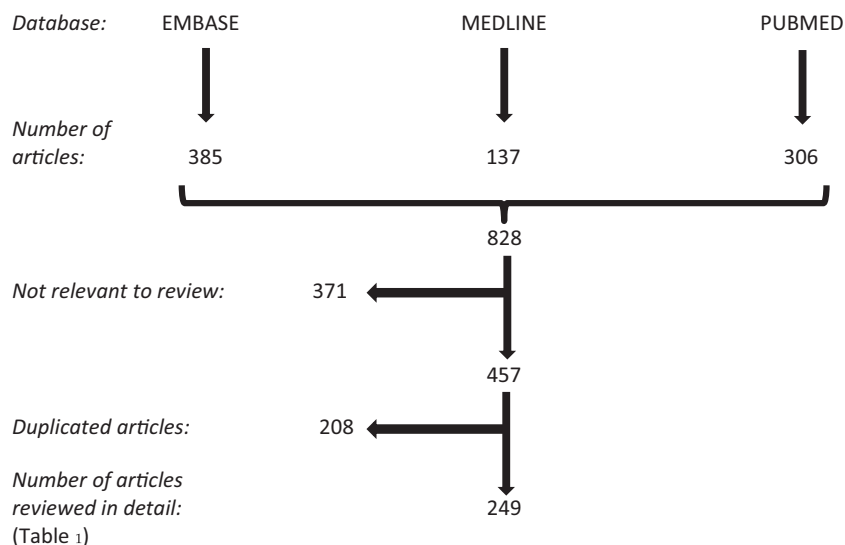
Type of study	Number of papers
<i>Retrospective case series</i>	
Radiotherapy alone	2
Radiotherapy and surgery	11
Radiotherapy and chemotherapy	1
Radiotherapy, surgery and chemotherapy	52
<i>Retrospective single centre case reports</i>	
Radiotherapy alone	2
Radiotherapy and surgery	0
Radiotherapy and chemotherapy	1
Radiotherapy, surgery and chemotherapy	4
<i>Prospective studies</i>	
Radiotherapy alone	1 (single centre)
Radiotherapy and surgery	6 (all single centre)
Radiotherapy and chemotherapy	4 (all single centre)
Radiotherapy, surgery and chemotherapy	46 (14 multicentre studies)
Letters to the editor	15
Systematic reviews	4
Reviews of the role of radiotherapy in MPM	21
Reviews of management of MPM	26
Technical studies/radiotherapy planning studies	53

## Literature review

### Radiotherapy in the context of EPP

The traditional aim of surgery for MPM has been to achieve macroscopic complete resection (MCR), however, this goal is made very challenging by the infiltrative growth pattern of MPM which often involves the fissures and surrounding thoracic structures. Neoadjuvant chemotherapy is often given with the aim of down staging the tumour and increasing the likelihood of a MCR, but local disease recurrence remains a considerable clinical problem [11–13]. Therefore, even though MPM is classically regarded as a radioresistant tumour, post-operative hemithoracic radiotherapy for local control has been an integral part of the treatment approach for decades [11,14,15].

In the context of EPP, delivery of adjuvant radiotherapy is facilitated by the removal of the ipsilateral lung and the subsequent elimination of its dose-constraint. Despite this relative advantage, the remaining target volume for treatment is large and complex,



**Fig. 1.** Overview of the literature search.

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