



Review

Radiotherapy for the treatment of pain in malignant pleural mesothelioma: A systematic review



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ABSTRACT

Radiotherapy is commonly used to treat pain in malignant pleural mesothelioma (MPM). The purpose of this systematic review is to examine the evidence for this practice. Medline (1946–2013), Embase (1974–2013) and Central (The Cochrane Library Issue 9, 2012) databases were searched. Eligible studies met the following criteria: MPM (histological or radiological diagnosis), radiotherapy given with the intent of improving pain, response rates to radiotherapy reported, dose and fractionation reported and the relationship between radiotherapy and pain response explored. All studies had independent review and were graded according to evidence level. Eight studies met the eligibility criteria. Two studies were prospective single arm phase II studies while the remainder were retrospective case series. All were graded as either Level 2 or Level 3 evidence. Due to marked heterogeneity among studies, quantitative synthesis of results was not possible. No high quality evidence currently exists to support radiotherapy in treating pain in MPM. Studies focusing on clear pain endpoints and improving target delineation are needed. Such studies should also use modern radiotherapy techniques and concentrate on dose escalation.

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1. Introduction

In 2009, over 2500 patients were diagnosed with MPM in the UK. The global incidence is not known but has been estimated at 14,200 per year [1]. The most common symptoms in MPM are pain and breathlessness though the reported incidence of pain varies from 25% to 90% [2–5].

The cause of the pain in MPM is often multifactorial. It may be caused by infiltration of the intercostal nerves by tumour and/or due to surgical procedures (pleural biopsy, thoracotomy etc.) [6]. Furthermore, mesothelioma may also invade bone causing significant pain. Therefore, the pathophysiology of pain in MPM is generally mixed: a combination of bone and neuropathic pain. As a result, patients are often on multiple analgesics such as non steroidal anti inflammatory drugs (NSAIDs), opioids, paracetamol, adjuvant analgesics for neuropathic pain as well as topical agents such as lidocaine patches [7]. Cordotomy is occasionally performed for these patients, however this is not widely available [6,8]. There is an urgency for patients with MPM to receive optimal pain control.

In terms of oncological interventions for treating pain in MPM, the armamentarium is limited. Surgery, chemotherapy and radiotherapy have all been studied in this disease. Surgical studies have tended to focus on long term tumour control rather than symptom improvement. Chemotherapy studies have generally been disappointing though two studies have shown a survival advantage [9,10].

Radiotherapy is effective at palliating many symptoms in cancer patients, especially cancer related bone pain [11]. Although precise data on the utilisation of radiotherapy in treating pain in MPM is unknown, it is frequently used for this purpose. However, the evidence supporting its use has not been clearly established [7].

This systematic review examines the evidence supporting the use of radiotherapy in treating pain in patients with MPM.

2. Materials and methods

Ethical approval was not required for this systematic review. The following databases were searched electronically: Medline (1946–2013), Embase (1974–2013) and CENTRAL (The Cochrane Library Issue 9, 2012). The keywords and search strategy are outlined in Appendix 1. The date of the last literature search was 5th February 2013.

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2.1. Eligibility criteria

2.1.1. Studies which met the following criteria were eligible

- MPM diagnosed histologically or radiologically.
- Radiotherapy given with the intent of improving pain.
- Documentation of the dose and fractionation of radiotherapy given.
- Response rates to radiotherapy reported.
- All types of study design potentially eligible.
- Studies published in English language.
- Prospective assessment of pain response desirable but not essential.

2.2. Appraisal process

Titles and abstracts of all the articles were reviewed independently by two authors (NM and BL). If the articles were thought to be potentially relevant, in accordance with the eligibility criteria, they were retrieved in whole. These were also reviewed independently by NM and BL. If both authors agreed that the articles met the eligibility criteria, they were included in this review. Where there was disagreement, the papers were discussed and a consensus reached. If there was doubt as to whether an article should be included or not, the primary authors were contacted to see if further information was available which might help to decide whether the study should be included or not.

The potential for quantitative synthesis and meta-analysis was assessed. However, due to the small number of papers, limited reported information in many studies and varying primary endpoint measures, quantitative synthesis of results was not possible. Therefore, the salient findings of each paper are presented.

3. Results

The following number of articles was retrieved: 462 (Medline), 1007 (EMBASE) and 11 (Central). The literature search results are shown in Fig. 1. Following the appraisal process described, eight articles were eligible.

Articles which met the eligibility criteria are shown in Table 1. Key aspects of each study are detailed. It is noted that no patients in any of the studies received pemetrexed based chemotherapy.

Excluded articles are shown in supplementary Table 1; [30–39]. Most were excluded as they either did not examine whether radiotherapy improved pain control in MPM or they did not document response rates. Therefore, these studies were excluded from this review.

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2013.11.004>.

In the majority of studies, pain response was assessed via retrospective case note review [2–4,12–14]. Pain scores were only assessed prospectively in two studies [15,16]. Patient numbers ranged from 19 to 189. All the studies are from single institutions with no multi centre studies performed. Dose and fractionation ranged from 8 Gy in 1 or 2 fractions to 60 Gy in 30 fractions. The reported benefit ranged from no benefit seen to 69% response [2,16].

4. Discussion

Based on the studies presented in this review, the evidence for radiotherapy in treating pain in mesothelioma ranges from Level 2 to 3 [17]. Therefore, firm recommendations on the role of radiotherapy in the relief of pain in MPM cannot be made. Due to a combination of poor study design and small numbers of patients,

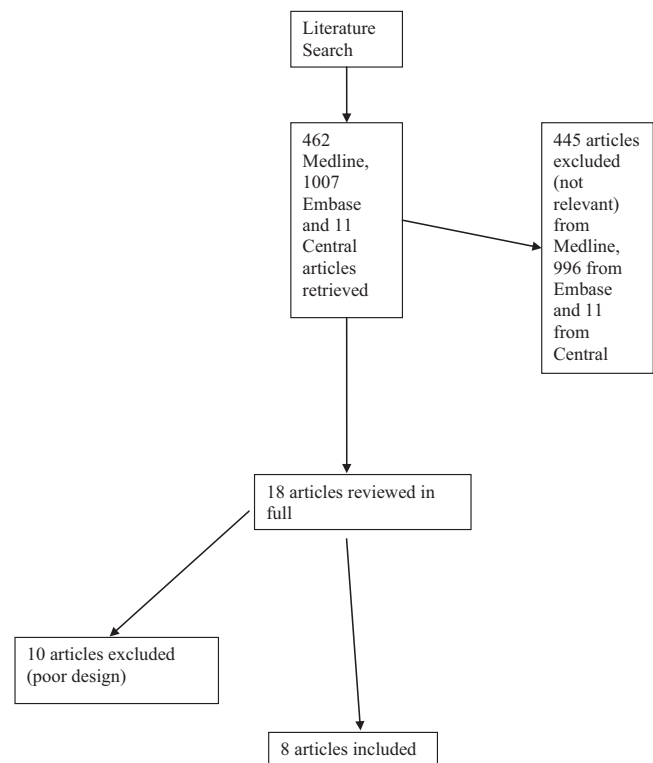


Fig. 1. Literature search results.

none of the studies fully examine the role of radiotherapy in the treatment of pain in MPM. Indeed, in four of the eight studies, assessment of pain response was retrospective and in two of the other studies, it is not clear as to how the reported response rate was derived [2–4,12–14]. These papers would have benefited from a prospective evaluation of pain response. The studies included in this review present little data on toxicity which would obviously be an essential requirement for future studies.

In the studies included in this review, reported response rates vary from no benefit seen to 69% [2,16]. Bissett et al's study provides the strongest evidence for radiotherapy in this setting [15]. This prospective study used clear measures of pain response and reported a 68% response rate. However, hemithoracic irradiation is rarely used nowadays due to concerns over toxicity. The only other study which assessed pain response prospectively was limited by the fact that 27 of the 47 patients in the study had no pain at study entry [16]. Therefore, showing any improvement in this group would be difficult and it is not surprising that this study did not show a benefit in pain scores after irradiation.

The most recent study in this review by Jenkins et al. is to be commended since response was evaluated with a CT scan two months after treatment [4]. However, the study is limited by the lack of validated pain assessment tools. Two ongoing randomised phase III UK trials assessing the role of prophylactic drain site irradiation are prospectively assessing pain response [18,19].

Although there is limited evidence to support radiotherapy for pain in MPM, it is recommended by the British Thoracic Society (BTS) as well as the European Respiratory Society and the European Society of Thoracic Surgeons (ERS/ESTS) [20,21]. However, the lack of strong evidence suggests that further work examining radiotherapy for pain in MPM is needed.

Studying the role of radiotherapy in MPM is challenging. Firstly, it is a cancer that is associated with a poor survival [3,12]. Even if patients do achieve a benefit in terms of pain response, this may be offset by a significant decline in performance status [15]. In these

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