



## Original Research Article

## Prophylactic procedure tract radiotherapy for malignant pleural mesothelioma: A systematic review and meta-analysis

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## ABSTRACT

**Background and purpose:** Malignant pleural mesothelioma (MPM) is an aggressive cancer with a propensity for seeding procedure tracts, leading to symptomatic metastases. There is conflicting evidence on the value of prophylactic procedure tract radiotherapy in reducing tract metastases. We performed a systematic review and meta-analysis to estimate the benefit of radiotherapy in this setting.

**Materials and methods:** Electronic databases were searched to January 1, 2018 for prospective randomized control trials with prophylactic procedure tract radiotherapy as the intervention arm. Pooled odds ratios and 95% confidence intervals were calculated using a random effects model. Study heterogeneity was assessed using the I<sup>2</sup> statistic, and publication bias was evaluated by funnel plot and Egger's regression model.

**Results:** Five studies were included for meta-analysis. Prophylactic radiotherapy did not have a statistically significant reduction on the risk of procedure site recurrence, with a pooled relative risk of 0.69 (95% CI 0.33–1.43). There was moderate heterogeneity between trials. All trials were assessed as moderate or high risk of bias overall.

**Conclusion:** This systematic review has confirmed that there is no role for prophylactic procedure tract radiotherapy in MPM. In the absence of effective prophylactic procedures, patients need to be monitored closely, and palliative interventions delivered in a timely manner to reduce morbidity associated with procedure tract metastases.

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## 1. Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer, with a five year relative survival of only 5.8% [1]. Australia and the United Kingdom have the highest annual rates of disease with approximately 30 cases per million, though epidemiological data is not available for many countries [2].

MPM is diagnosed by cyto-histological confirmation from either pleural fluid or tissue. The latter requiring large bore pleural procedures ranging from CT-guided core biopsy, thoracoscopy, video-assisted thoracoscopic surgical interventions, or open pleural biopsy. At diagnosis over 90% patients report dyspnoea due to malignant pleural effusion, which is usually palliatively managed from the outset with repeated pleurocentesis, continuous indwelling catheter drainage, or talc pleurodesis. More rarely pleurectomy is attempted.

MPM however has a propensity to spread along needle or thoracic trocar procedure tracts to skin puncture or incision sites, with tumour cell seeding leading to symptomatic subcutaneous metastases in up to 51% of patients [3,4]. Prophylactic procedure tract radiation therapy has been utilised with the aim of reducing the incidence of these metastatic (or implantation) deposits. Although in vitro studies suggest that mesothelioma cells are radiosensitive [5], and procedure tract radiation therapy is invariably safe and technically feasible, evidence from observational studies and randomised control trials has been conflicting, leading to uncertainty regarding its efficacy. This is reflected in variation in international treatment recommendations [4]. Given the uncertainty, we performed a systematic review and quantitative meta-analysis of the role of prophylactic radiation therapy to procedure tract sites in MPM.

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## 2. Methods

### 2.1. Search strategy and data sources

We followed the preferred reporting items in systematic reviews and meta-analyses (PRISMA) guidelines [6]. MEDLINE, EMBASE, CENTRAL, and PubMed were searched from inception to January 2018 by two reviewers (M.T. and S.B.). The search included the terms 'mesothelioma' and 'radiation therapy' or 'radiation therapy'. Reference lists of included articles, systematic reviews, and narrative reviews were hand searched.

The International Clinical Trials Registry Platform, [Clinicaltrials.gov](http://Clinicaltrials.gov), European Union Clinical Trials Register, and Australian New Zealand Clinical Trials Registry were searched for unpublished trials. There were no language restrictions. Disagreements were resolved by a third reviewer (M.J.S.).

### 2.2. Study selection and data extraction

Eligible studies were included if they described: (1) Prospective randomization; (2) An intervention arm of prophylactic radiation therapy to procedure sites in mesothelioma patients; (3) A control arm of no prophylactic radiation therapy or sham radiation therapy; (4) Rates of mesothelioma recurrence at procedure sites.

### 2.3. Data extraction

Two reviewers (M.T. and S.B.) extracted data from included studies. Last name of first author, year of publication, country of origin, inclusion and exclusion criteria, intervention and control treatments, sample size of intervention and control arms, total sample size, survival, adverse events, quality of life, and study design methodology were extracted.

### 2.4. Risk of bias assessment

Risk of bias was assessed by two reviewers (M.T. and S.B.). The assessment was conducted using the Cochrane Collaboration's tool for assessing risk of bias [7]. Disagreements were resolved by a third reviewer (M.J.S.).

### 2.5. Statistical analysis

Pooled relative risk and 95% confidence intervals of risk of mesothelioma recurrence at intervention sites was calculated using the random-effects model of DerSimonian and Laird [8]. Heterogeneity across included studies was assessed using the  $I^2$  statistic [9]. Publication bias was assessed by visual inspection of funnel plots, and using Egger's regression model [10]. A two tailed  $p < 0.05$  was used as the threshold for statistical significance. All analyses were performed using Comprehensive Meta-analysis (version 2.2), Englewood, NJ, USA (2005).

## 3. Results

The search strategy identified 4398 studies, from which 5 randomized controlled trials were included for meta-analysis (Fig. 1) [11–15]. One included study has been reported in abstract form only [15].

Table 1 shows the characteristics of the included studies. Patient characteristics and inclusion criteria were similar across trials, however there was variability of timing and dosage of the prophylactic radiation therapy. All trials were designed to detect differences in procedure site recurrence rates.

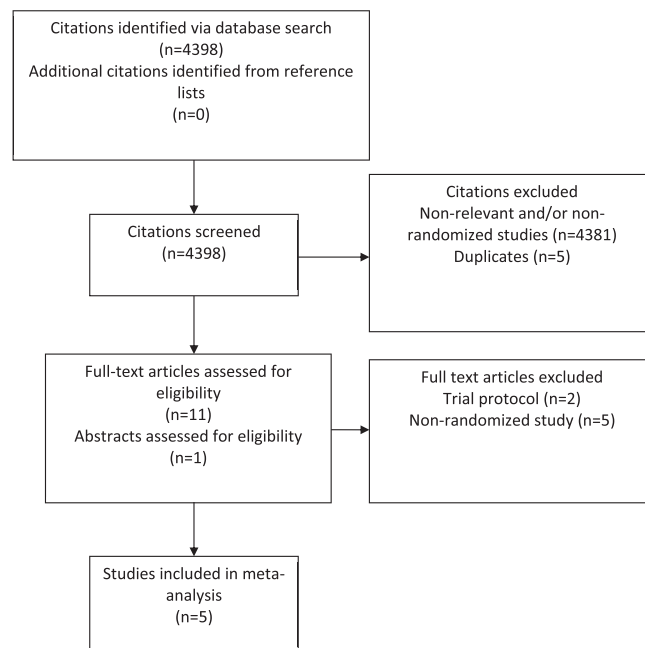


Fig. 1. Flowchart of search strategy.

Two trials reported on overall survival [11,14]. The reporting of adverse events was variable between trials. Only one trial reported a single grade 3 adverse event of radiation dermatitis [15], with the remaining trials reporting grade 2 or lower adverse events only. Two trials reported quality of life measures [13,14].

Meta-analysis of survival, adverse events, and quality of life measures was not attempted due to variability in reporting. Table 2 shows the risk of bias assessment, with all trials assessed as either moderate or high risk of bias overall.

Fig. 2 shows the meta-analysis of 5 trials with a total sample size of 737 patients, on the risk of procedure site mesothelioma recurrence with prophylactic radiation therapy. Prophylactic radiation therapy did not have a statistically significant reduction on the risk of procedure site recurrence, with a pooled relative risk of 0.69 (95% CI 0.33–1.43),  $p = 0.32$ . There was moderate heterogeneity between trials, with  $I^2 = 41.0$ . There was no evidence of publication bias on visual inspection, or Eggers test  $p = 0.69$ .

## 4. Discussion

Our systematic review found that there is no significant benefit of prophylactic procedure tract radiation therapy in MPM patients.

There was however significant heterogeneity in radiation therapy dose, technique and timing in the included trials. Four studies treated patients with 21 Gy in three fractions on consecutive working days, using clinical mark-up and electron or photon therapy with energies adapted to patient anatomy and procedure tract topography [11,13–15]. No study however used modern CT-simulation to define target volumes, which may limit applicability to current clinical settings. One study delivered 10 Gy in a single fraction using 9 MeV electrons [12]. Previous reviews have argued that this dose is suboptimal [16–18]. The uniform use of 9 MeV may have also led to underdosing in patients with thicker chest walls. One of the trials has been criticised for using a field size of 6 cm [13], with an argument that this was relatively small, explaining the lack of effect [17]. Delivery of radiation therapy ranged from 10 to 42 days post intervention, within the maximum two month latency from intervention thought to be necessary for reduction of chest wall metastasis recurrence [17]. The secondary

**Table 1**  
Characteristics of included trials.

Study	Year	Country of origin	Age (mean)	Prophylactic radiation therapy (RT) (n)	No prophylactic RT (n)	Recurrence with prophylactic RT (%)	Recurrence without prophylactic RT (%)	Median time to metastasis from intervention with RT	Median time to metastasis from intervention without RT	Inclusion/exclusion criteria	Procedure type	Intervention	Control	Median Survival Intervention	Median Survival Control	Adverse Events	Quality of Life
Boutin et al. (1995)	1995	France	66 (mean)	20	20	0 (0%)	8 (40%)	Not applicable	6 months	Diagnosis of mesothelioma; Thoracoscopy and tract biopsy within one month; life expectancy >3 months	Thoracoscopy trocar/chest tube, puncture (not otherwise specified)	Prophylactic EBRT; 21 Gy in 3 fractions, 12.5–15 MeV; Given after wound healing, 10–15 days post thoracoscopy	Nil EBRT	14 months	8 months	Adverse events of EBRT arm described only. Grade of events not described. Skin discoloration in 100% of EBRT arm. 0% inflammation or edema. Other adverse events not described	Not described
Bydder et al. (2004)	2004	Australia	70 (mean)	28	30	2 (7%)	3 (10%)	Not reported	Not reported	Adults with pathological diagnosis of mesothelioma; Identifiable procedure site	Thoracic drain/thoracoscopy. FNA. Abrams needle	Prophylactic EBRT; 10 Gy in 1 fraction, 9MeV; Given within 15 days of procedure	Nil EBRT	Not reported	Not reported	Adverse events of EBRT arm described only. Grade 1 adverse events not described. Nil grade 2–4 adverse events in EBRT arm	Not described
O'Rourke et al. (2007)	2007	UK	70 (median)	31	30	7 (23%)	3 (33%)	2.4 months	6.4 months	Pathological diagnosis of mesothelioma; Procedure performed within 21 days of trial enrolment; Exclusion of prior radiation therapy or prior chemotherapy, expected survival <3 months	Pleural biopsy, chest drain, thoracoscopy	Prophylactic EBRT; 21 Gy in 3 fractions, 9–12 MeV or 250kV photons; Given within 21 days of procedure	Best Supportive Care	Not reported	Not reported	Adverse events of EBRT arm described only. Grade of events not described. 10% skin discoloration; 3% nausea and vomiting; 3% nausea, anorexia, chest discomfort; 16% patient self report of any side effect	Hospital Anxiety and Depression questionnaire. Increased depression in BSC arm (p = 0.028). Increased anxiety in EBRT arm (p = 0.029)
Clive et al. (2016)	2016	UK	70 (mean)	102	101	9 (9%)	16 (16%)	179 days	224 days	Pathological diagnosis of mesothelioma; Large bore pleural thoracotomy, procedure within 35 days; Exclusion of age <18 years, pregnant or lactating, prior radiation therapy, survival <4 months	Thoracoscopy, video-assisted thoracoscopic surgery, thoracotomy, indwelling pleural catheter	Prophylactic EBRT; 21 Gy in 3 fractions; Given within 42 days of procedure	Deferred palliative EBRT to recurrence site; 21 Gy in 3 fractions; Given within 35 days of recurrence	357 days	365 days	Within 3 months and > 3 months adverse events described for patients receiving EBRT; 54% grade 1 and 4% grade 2 skin toxicity within 3 months; 52% grade 1 and 1% grade skin toxicity after 3 months; 11% nausea within 3 months; 4% nausea after 3 months; 39% fatigue within 3 months; 23% after 3 months; 1% anorexia within 3 months; 2% pain within 3 months	Chest pain VAS; QOL-C30 score; EQ-5D score; Morphine equivalent dose score. Nil significant differences between arms

Table 1 (continued)

Study	Year	Country of origin	Age (median)	Prophylactic radiation therapy (RT) (n)	No prophylactic RT (n)	Recurrence with prophylactic RT (%)	Recurrence without prophylactic RT (%)	Median time to metastasis from intervention with RT	Median time to metastasis from intervention without RT	Inclusion/exclusion criteria	Procedure type	Intervention	Control	Median Survival Intervention	Median Survival Control	Adverse Events	Quality of Life
Bayman et al. (2017)	2017	UK	73 (median)	186	189	6 (3%)	10 (5%)	Not reported	Not reported	Diagnosis of mesothelioma; Chest wall intervention; Able to start radiotherapy within 42 days; Exclusion of thoracotomy, previous radiotherapy, currently receiving chemotherapy	Video-assisted thorascopic surgery, open surgical biopsy, thoracoscopy, chest drain	Prophylactic EBRT, 21 Gy in 3 fractions; Given within 42 days of procedure	Nil EBRT	Not reported	Not reported	Adverse events of EBRT arm described only. 52% grade 1 skin toxicity; 10% grade 2 skin toxicity; 0.5% grade 3 radiation dermatitis. Nil other grade 3 or higher radiotherapy-related adverse events	Not reported

per protocol analysis of the SMART trial, which excluded patients with serious protocol deviations, showed that procedure tract metastasis incidence was significantly lower in the prophylactic radiotherapy group than in the deferred group (6% vs. 16%) [14]. This suggested that adequate radiation therapy may have an impact on metastatic deposit development, though the ability to deliver the trial protocol in real clinical settings is untested.

Radiation therapy appeared to be relatively well tolerated, with no grade 4 or greater adverse events. Skin toxicity was the most common radiotherapy-related adverse event, with rates of Grade 1 toxicity in up to 54% and Grade 2 in up to 10.2% of patients. One trial reported a single Grade 3 radiation dermatitis (0.5%) [15]. Other reported acute toxicities included lethargy, nausea, loss of appetite and chest discomfort. Late toxicities included subcutaneous tissue toxicity, nausea and lethargy.

Median time from intervention to chest wall metastasis was reported in three trials [11,13,14]. This ranged from 2.4 to 5.8 months in the prophylactic radiation therapy group, and 6 to 7.4 months in the control group. No significant difference was seen in the time to development of metastasis between the groups in any trial.

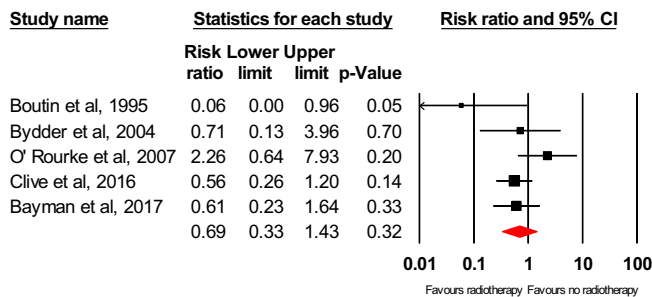
Two trials reported the location of chest wall recurrence in relation to the radiation field [13,14]. One reported that 75% of metastasis occurred overlying or adjacent to the intervention tract site [13]. The other reported that the minimum distance between the intervention site and the edge of the metastasis was longer in the prophylactic radiation therapy group compared to the control group (mean 4.6 cm vs. 1.3 cm) suggesting a radiation field effect [14].

The incidence of procedure tract metastasis varies widely in the literature. Larger bore procedure tracts have been associated with an increased risk of tract metastasis (4% for image guided core needle biopsy versus 22% for surgical biopsy) [19], though this correlation was not demonstrated in the included trials. Three studies reported the rates of metastases for different baseline procedures, including FNA, Abrams needles, thoracic drains, thoracoscopy, and open thoracic surgery [12–14]. There was no statistically significant association between type of baseline procedure and development of metastatic deposits. There was heterogeneity in interventions included in each trial, and incomplete data in one trial [13]. The difference in incidence in the literature is likely explained by other factors, such as procedural technique, disease biology, systemic treatment and host factors.

MPM is associated with a poor prognosis and short lifespan. As such, treatment should be rationalised to maximise benefit and minimise patient inconvenience, time cost and potential side effects. There was significant heterogeneity in symptom assessment in the trials, with three reporting pain outcomes [13–15]. One utilised visual analogue scale (VAS) pain scores, and analgesia use to assess chest pain, with no difference found between the radiation therapy and control groups at baseline and during follow-up [14]. Another employed a swelling questionnaire for patients with metastatic deposits, with a 58% completion rate (seven patients) [13]. Two patients reported that the metastatic deposit was uncomfortable “quite a lot”, whilst one stated “not very much” and four “not at all”. The rate of symptomatic metastases in these trials was low (range 25–32%) [13,14], suggesting that a significant number of patients may not require palliation during their disease course. The third trial recorded VAS pain scores at the time of development of chest wall metastases [15]. The evaluable patients reported a median score increase of 0, and a mean increase of 13.3 compared to baseline. This is suggestive of a right skewed distribution, with a significant proportion of patients having little to no increase in pain. There was no comparison of pain scores between those who received prophylactic procedure tract radiation therapy, and those who did not, which is a

**Table 2**  
Assessment of risk of bias.

Study	Sequence generation	Allocation concealment	Blinding of patients & staff	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risks of bias
Boutin et al. (1995)	Not described. Unclear risk	Not concealed. High risk	Not blinded. High risk	Not described. High risk	Not described. Unclear risk	Adverse events not fully described. Unclear risk	–
Bydder et al, 2004	Not described. Unclear risk	Not concealed. High risk	Not blinded. High risk	Not described. High risk	Not described. Unclear risk	Adverse events not fully described. Unclear risk	Intention to treat analysis used. Low risk
O' Rourke et al. (2007)	Centralized computer sequence generation. Low risk	Not concealed. High risk	Not blinded. High risk	Not described. High risk	87% follow up. Low risk	Adverse events partially described. Low risk	Intention to treat analysis used. Low risk
Clive et al. (2016)	Centralized computer sequence generation. Low risk	Not concealed. High risk	Not blinded. High risk	Not blinded. High risk	94% follow up. Low risk	Adverse events described. Low risk	Intention to treat analysis used. Low risk
Bayman et al. (2017)	Centralized computer sequence generation. Low risk	Not concealed. High risk	Not blinded. High risk	Not blinded. High risk	Not described. Unclear risk	Adverse events described. Low risk	Intention to treat analysis used. Low risk



**Fig. 2.** Risk of procedure site recurrence with prophylactic radiation therapy versus no prophylactic radiation therapy.

clinically relevant question. This may become available with the full publication of the Prophylactic Irradiation of Tracts (PIT) data.

Two trials reported health-related quality of life [13,14]. One found no significant differences between the treatment groups in the 12 month follow-up period [14]. Conversely, the other identified significantly worse anxiety levels in the prophylactic radiation therapy group, and worse depression in the control group [13]. These results were based on only 39 of the 61 patients, and due to the natural history of the disease, these patients completed less than half of the required questionnaires. These results must therefore be interpreted with caution. The lack of difference in patient-centered outcomes such as pain control and quality of life, suggests that patients may be best managed with close monitoring of intervention sites, with timely delivery of palliative radiation therapy or best supportive care for metastatic deposits.

None of the included trials were sufficiently powered to determine whether certain subgroups would benefit from prophylactic procedure tract radiation therapy, however there were trends within the SMART trial that may warrant further investigation [14]. Those with epithelioid-only histology appeared to derive more benefit from prophylactic radiation therapy than other histologic subtypes. Epithelioid histology is associated with improved survival for all stages of malignant mesothelioma, and it is postulated that this subtype is more responsive to treatment. The patients who did receive chemotherapy also had a reduced incidence of procedure tract metastases in the prophylactic radiation therapy group suggesting a synergistic contribution of chemotherapy at the site of chest wall intervention.

One trial reported the health economics of prophylactic radiation therapy [14]. No significant differences were seen in mean total cost or mean QALYs of radiation therapy in the prophylactic

setting versus deferred radiation therapy at the time of metastatic nodule development.

## 5. Conclusion

This systematic review has confirmed that there is no role for prophylactic procedure tract radiation therapy in MPM. Although patient selection and treatment technical factors remain confounding variables in several of the trials examined, prophylactic radiotherapy does not appear to reduce the rate of procedure tract metastases. Furthermore, there do not appear to be symptom or quality of life benefits, which are of particular importance in this aggressive disease. There is still some uncertainty regarding whether certain subgroups derive a greater benefit from prophylactic procedure tract radiotherapy. The final publication of the PIT study data may clarify this matter. Procedure tract metastases however remain a potential morbidity for MPM patients. In the absence of effective prophylactic interventions, patients need to be monitored closely, and managed promptly with the development of symptoms.

## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2018.09.004>.

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