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Prophylactic radiotherapy for procedure tract metastases (PTMs) in mesothelioma; a review

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Abstract

Purpose of review: Malignant pleural mesothelioma is an aggressive malignancy with a very poor prognosis. The majority of patients require pleural procedures for diagnostic or fluid management purposes. Damage to the pleura during these procedures can lead to procedure tract metastases (PTMs), with increasing risk from larger interventions. Prophylactic radiotherapy to these sites is a controversial topic with conflicting results from trial data. In this review we summarise the recent evidence.

Recent findings: Four RCTs have been published on this topic, with another in follow-up. The earliest, from a cohort of 40 patients, strongly advocated the use of prophylactic radiotherapy. More recent trials, most notably the SMART trial (which randomised over 200 patients) did not demonstrate any benefit, especially when patient report symptoms and cost-effectiveness are considered. Certain subgroups demand further investigation, such as those not receiving systematic chemotherapy or with surgical intervention sites. The soon to be published PIT trial may help to further clarify best practice.

Summary: Recent studies have shown that prophylactic radiotherapy should not be routinely used to prevent PTMs in mesothelioma. Instead patients should undergo careful clinical follow up to ensure PTMs are identified and treated promptly to minimise symptoms.

Keywords; mesothelioma, prophylactic, radiotherapy, metastasis

Introduction

Malignant pleural mesothelioma (MPM) is an aggressive and invariably fatal malignancy. Average survival is 9-14 months from diagnosis and patients often experience disabling symptoms of pain and breathlessness [1]. Patients with mesothelioma usually require pleural interventions for tissue diagnosis and fluid management. Prophylactic radiotherapy to intervention sites has previously been recommended to reduce the occurrence of procedure-tract metastases (PTMs). There has been significant equipoise about the efficacy of prophylactic radiotherapy, reflected in conflicting recommendations from international guidelines. The aim of this review was to summarise the recent literature surrounding this topic.

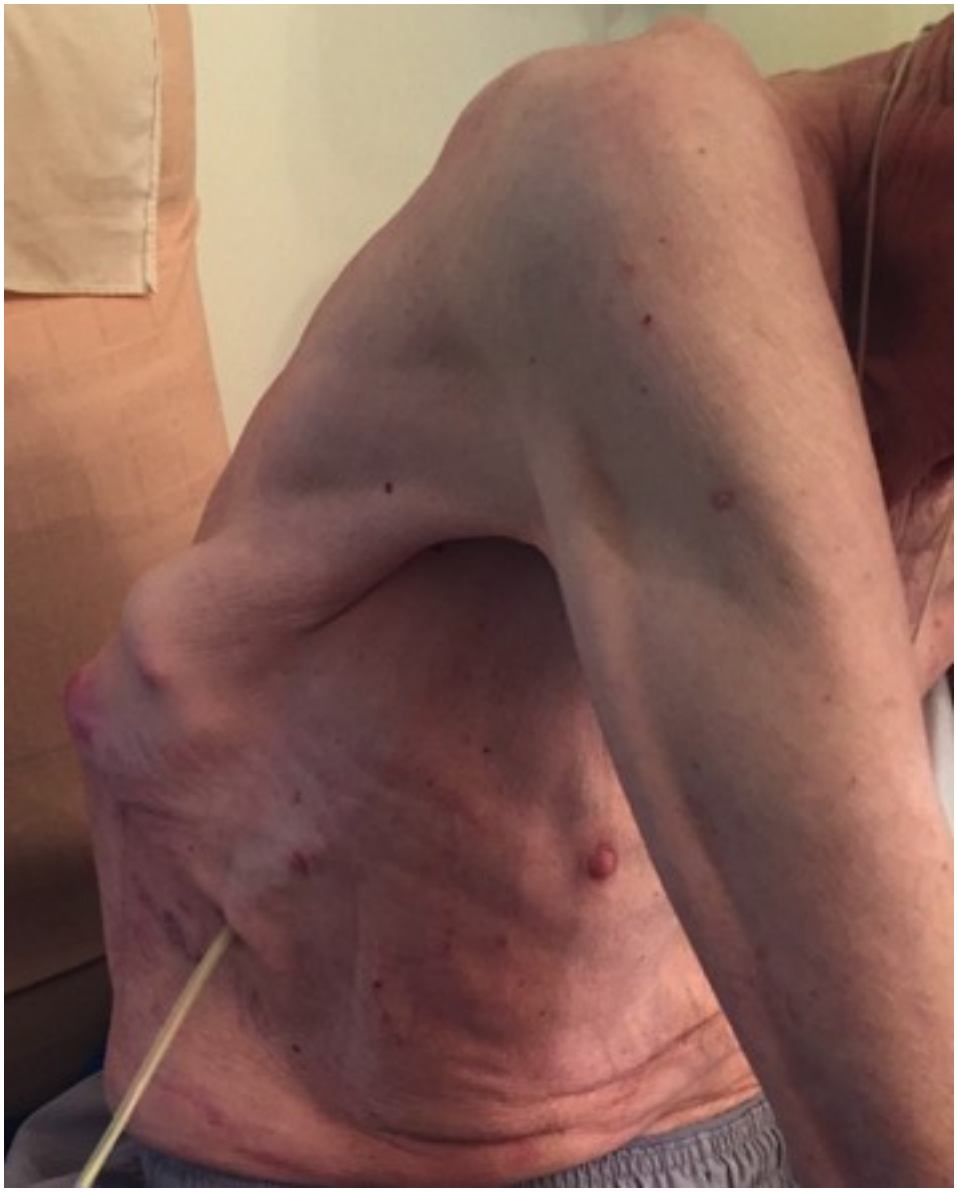
Procedure Tract Metastases

The diagnosis of MPM can be challenging. On computerised tomography (CT) scans the tumour can mimic other causes of both malignant and benign pleural thickening. The diagnostic yield from pleural fluid cytology in mesothelioma is notoriously low [2]. Resultantly, patients usually require a CT guided biopsy, thoracoscopy or Video Assisted Thorascopic Surgery (VATS) in order to obtain tissue for histological confirmation of the diagnosis. Furthermore, once a diagnosis of MPM is made, patients may experience troubling breathlessness due to the re-accumulation of pleural fluid, necessitating therapeutic pleural aspirations, chest drain or indwelling pleural catheter (IPC) insertion to manage their symptoms.

A complication of instrumentation of the pleura in MPM is seeding of malignant cells along the procedural tract, which can result in the development of PTMs. These subcutaneous nodules (see Figure 1), may develop many months after the initial procedure and can be painful. It is not clear whether they develop due to deposition of pleural fluid containing tumour cells into the subcutaneous tissues during the pleural procedure or whether disruption to the tumour on the pleural surface during the intervention stimulates the tumour to grow along the procedure tract (2).

The incidence of PTM in patients with MPM varies widely and is likely due to a number of factors. A retrospective case series published by Agarwal et al demonstrated that the risk of PTM development was related to the size of chest wall incision. The incidence of PTM after small bore procedures was minimal (3.6 % of patients developed a PTM after thoracentesis) but increased with more invasive procedures (16% following thoracoscopy and 24% after a thoracotomy) [3]. It is probable that other procedural, host and tumour factors also contribute an individual's risk of a PTM developing, which may explain the disparity in the incidence of PTMs in the literature.

Figure 1; Patient with a large painless procedure tract metastasis and indwelling pleural catheter.



In vitro studies have demonstrated that mesothelioma tumour cells are highly radiosensitive [4]. In spite of this, the large treatment volumes and substantial toxicity to other thoracic organs required for radical treatment of MPM precludes its use for this purpose [5]. However, prophylactic radiotherapy to the tracts of previous thoracic interventions to prevent subsequent development of PTM is feasible but conflicting results from three small RCTs and a number of case series evaluating its efficacy has resulted in a long running debate about its efficacy (Table 1). This clinical equipoise is reflected in substantial variation in clinical practice guidance from different organisations around the world (see Table 2).

Table 1. Summary of literature

Author, year	Study Type	Number of patients	Pleural procedure type	Radiotherapy regimen - max time from procedure to RT - Dose and fractionation - Energy - Field size	PTMs in controls	PTMs in intervention group	Odds ratio [95% CI] (p-value)
Randomised controlled trials							
Boutin, 1995 [6]	RCT	40	LAT- 40	15 days 21Gy in 3 fractions 12.5 to 15 MeV 16 to 100cm^2	8/20 (40%)	0/20 (0%)	0.04* [0.01-0.70] p<0.01
Bydder, 2004 [7]	RCT	43 (58 sites)	CD/LAT- 22 FNA- 27 Abrams- 9	15 days 10Gy in 1 dose 9 MeV ND	3/30 (10%)	2/28 (7%)	0.70* [0.11-4.49] p= 0.53
O'Rourke, 2007 [8]	RCT	61	CD-15 PB- 27 LAT- 16 Un- 3	21 days 21 Gy in 3 fractions 9-12 MeV 6 cm diameter circle	3/30 (10%)	4/31 (13%)	1.33* [0.27-6.53] p=0.75
Clive, 2016 [9]	RCT	203	Wide CD- 3 LAT- 74 Thor- 9 VATS- 91 IPC- 25 CGB- 1	42 days 21 Gy in 3 fractions Variable >7 cm diameter	16/101 (16%)	9/102 (9%)	0.51 [0.19-1.32] p= 0.14
Bayman, 2016 [10]	RCT	374	Awaited	42 days 21 Gy in 3 fractions Single electron field Trial led	Awaited	Awaited	Awaited
Case series and cohort studies							
Low, 1995 [11]	Retrospective case series	20 (from 38 intervention sites)	ND	15 days 21 Gy in 3 fractions 140 or 250 KV 4cm diameter	n/a	0/38 (0%)	n/a
Cellerin, 2004 [12]	Retrospective cohort study	58	ND	Variable	12/25 (48%)	7/33 (21%)	0.29* [0.09-0.92] p=0.04
West, 2006 [13]	Retrospective case series	37	ND	ND 21 Gy in 3 fractions 10 MeV Variable	n/a	2/37 (5%)	n/a
Di Salvo, 2008 [14]	Retrospective case series	32	FNA- 21 TCentesis- 5 LAT- 5 PD- 1	Variable 21 Gy in 3 fractions 12 MeV 100 cm^2	n/a	0/32 (0%)	n/a
Metintas, 2008 [15]	Retrospective case series	212	CGB/PB- 135 LAT- 46 Thor- 31	n/a	28/212 (13%)	n/a	n/a
Kara, 2010 [16]	Retrospective case series	19	PB- 8 LAT- 6 Thor- 3 VATS- 8 PD/EPP- 7	27 days 21 Gy in 3 fractions 12 MeV Variable	n/a	0/19 (0%)	n/a
Froment, 2011 [17]	Retrospective cohort study	171	ND	36 days Various radiotherapy regimens	40/123 (33%)	6/48 (13%)	0.27* [0.12-0.76] P<0.01
Akmansu, 2013 [18]	Retrospective case series	27	ND	69 days Variable 4-15 MeV Variable	3/27 (12%)	n/a	n/a
Janssen, 2015 [19]	Retrospective case series	52	VATS- 53	40 days 21 Gy in 3 fractions 6-18 MeV Variable	3/53 (6%)	n/a	n/a

Table abbreviations; RCT- Randomised controlled trial, LAT- Local anaesthetic thoracoscopy, CD- Chest drain, FNA- Fine needle aspiration, TCentesis- Thoracocentesis, PB- Pleural biopsy, PD- Pleural decortication, EPP- Extrapleural pneumonectomy, Thor- Thoracotomy, VATS- Video assisted thoracoscopic surgery, IPC- Indwelling pleural catheter, CGB- CT guided biopsy, Gy= Gray, MeV=ND- Not documented, Un- Unknown, *- Odds Ratio not reported in primary paper but calculated from reported data.

Table 2: Recommendations regarding prophylactic irradiation of tracts from the current mesothelioma clinical practice guidelines

Guideline	Year	Prophylactic RT recommended?	Recommendation regarding prophylactic RT
British Thoracic Society Consensus Statement [20]	2007	Yes	'If good performance score and after more invasive procedures'
European Respiratory Society [21]	2010	No recommendation	'value of prophylactic radiotherapy is questionable'
National Comprehensive Cancer Network (NCCN) [22]	2016	Yes	'21 Gray in 3 fractions to surgical sites'
Journal of Thoracic Diseases [23]	2013	No	'Prophylactic radiotherapy… has no significant effect on changing the disease course'
European Society for Medical Oncology (ESMO) [24]	2015	Not unless part of a clinical trial	'probably best to recommend refraining from this procedure unless in the setting of a clinical trial'
Spanish Society of Medical Oncology (SEOM)	2011	No	'no sufficient evidence to definitively recommend it'

Effect of prophylactic radiotherapy on PTM incidence

The first randomised controlled trial (RCT) investigating the role of prophylactic radiotherapy in preventing PTMs in MPM was performed by Boutin et al in 1995 [6]. Forty patients were randomised to either receive 21 Gray in three fractions over 3 days to their thoracoscopy site, very soon (10-15 days) after thoracoscopy, or no radiotherapy. No PTMs were identified in the intervention group (0/20) compared to 8/20 (40%) in the control group, which led them to conclude that radiotherapy was not only safe but extremely effective in preventing PTMs. A retrospective case series published the same year appeared to support their findings (0 % vs 21 % PTM incidence in radiotherapy and non-radiotherapy groups) [11].

However, clinical equipoise remained, as the very high PTM incidence in the control arm of Boutin's study was not felt to reflect that seen by clinicians in everyday clinical practice. This led to the publication of an RCT [7] from Australia, which showed no significant difference in PTM incidence between the treatment and control arms. However, the radiotherapy regimen of a single 10 Gray dose was much lower than the 21 Gray used in the previous study and the overall PTM incidence in the trial was lower, probably because patients who had undergone small bore interventions (which are lower risk for PTM development) were included. In view of this and despite the negative finding of the trial, the authors continued to advocate the use of 21 Gray in 3 fractions of prophylactic radiotherapy for high risk pleural interventions to prevent PTMs.

Given the ongoing controversy, a further RCT was conducted in the UK by O'Rourke in 2007 [8]. This study randomised 61 patients with MPM who had undergone a recent pleural intervention to receive 21 Gray in 3 fractions within 21 days or no prophylactic radiotherapy. The inclusion of patients following small bore pleural procedures explains the lower overall incidence of PTMs (7/61) but not the lack of treatment effect of 13% versus 10% between the treatment and control arms respectively. The authors concluded that local radiotherapy should only be used after the development of a symptomatic PTM and not as prophylaxis.

Three systematic reviews of the literature have been performed, which included the above RCTs [5, 25, 26]. Although the RCTs are heterogeneous in terms of study design and radiotherapy regimens, when the data was pooled, no difference between treatment and control arms was demonstrated.

Since the publication of these trials there has been a shift in the management of MPM. Firstly, the majority of eligible patients are now offered palliative pemetrexed-based chemotherapy [27]. In addition, indwelling pleural catheters (IPCs) are increasingly used for pleural fluid management as opposed to standard chest drain with pleurodesis. The continuing equipoise around the efficacy of prophylactic radiotherapy, and the uncertainty regarding the potential impact of chemotherapy and IPCs on its efficacy, led to a desire from the mesothelioma community for further randomised data to clarify the situation further [25].

The recently published SMART trial aimed to reassess the role of prophylactic radiotherapy in modern MPM management and included more extensive symptom control, health related quality of life (HRQoL) and health economic assessment than the previous studies [9]. This UK based multi-centre RCT randomised patients to 'immediate' radiotherapy, within 42 days, or 'deferred' radiotherapy, where radiotherapy was performed only if PTMs developed. In order to account for the low incidence of PTMs seen in previous studies, the inclusion criteria involved only 'large-bore'

procedures (thoracoscopy, VATS, thoracotomy and, for the first time, indwelling pleural catheters). Twenty-one Gray in 3 fractions of radiotherapy was delivered and the field selected based on visible intervention sites with at least a 3cm margin and a minimum diameter of 7cm. Two hundred and three patients were randomised across 22 centres. The primary, intention to treat analysis after 12 months of follow up revealed no significant difference in the incidence of PTMs between the 'immediate' (9/102) and 'deferred' (16/101) groups (odds ratio (OR) 0·51 (0.19-0.32); p=0·14).

However, there were 11 protocol violations relating to radiotherapy delivery in the immediate radiotherapy group and the pre-defined per-protocol analysis demonstrated a marginally significant difference in PTM incidence between the treatment groups in favour of immediate radiotherapy (OR 0.33 (0.09-1.00) p= 0.04). This highlights that if prophylactic radiotherapy is to be delivered, accurate and timely administration is paramount. However, whether this is feasible for all-comers outside the context of a clinical trial is questionable. This, along with the lack of symptom or quality of life benefit (see later) led the SMART trial authors to conclude that routine use of prophylactic radiotherapy in all patients with MPM after a large bore intervention was not beneficial.

Effect of prophylactic radiotherapy on symptoms and quality of life

It is vital when considering the efficacy of prophylactic radiotherapy to consider the effect of the treatment and PTMs on the patient's symptoms and quality of life. Treatment of mesothelioma is palliative and the rigorous follow up of randomised trials may result in the detection of small, asymptomatic nodules which are not of clinical consequence to the individual. Hence the evaluation of patient centred secondary endpoints in conjunction with the incidence of chest wall nodules is critical.

The first RCT to include any patient reported outcome data was the O'Rourke study. Condition-specific questionnaires were completed by the 7 patients who developed PTMs of which three reported the PTM to be uncomfortable. Patients also completed the 'Hospital Anxiety and Depression' questionnaire during their 12 month follow up, although only 39/61 patients had usable data. They did identify significantly worse anxiety levels in the prophylactic radiotherapy group and worse depression in the control group although the small numbers in each analysis limits its interpretation.

The SMART trial examined symptom control, analgesia use and health-related quality of life (HRQoL) across the entire cohort and found no significant differences in any of these patient centred outcomes between the treatment groups during 12 month follow up. In fact, only one-third of PTMs were painful at the time of identification and no significant differences were seen in the pain scores or analgesia use of patients who developed a PTM between the treatment groups during their remaining follow up. The radiotherapy was well tolerated and no complications from delivery of radiotherapy to IPCs were identified.

Cost-effectiveness of prophylactic radiotherapy

The SMART trial is the only trial to date to evaluate the health economic impact of delivering prophylactic radiotherapy in mesothelioma. The mean total costs and QALYs of the two arms were comparable, resulting in no significant difference in the point estimate of the incremental cost-effectiveness ratio between the groups. Based on this data, delivery of prophylactic radiotherapy was not deemed cost effective although full health economic assessment of the SMART trial data is awaited.

Areas warranting further investigation

None of the published studies are sufficiently powered to conclusively evaluate whether prophylactic radiotherapy benefits specific subgroups of patients with MPM, however some potential signals were identified by the SMART trial, which may warrant further investigation.

Although it did not reach statistical significance, the SMART trial showed a trend for patients with epithelioid-only features on histology to benefit from prophylactic radiotherapy in terms of PTM incidence (6/71 (8%) in the immediate radiotherapy developed a PTM compared with 15/72 (21%) in the deferred arm (OR 0.35 (0. 11‑1. 04) p= 0. 057)). This is likely to be related to the improved survival and therefore duration of benefit in this group compared to those with other histological subtypes.

Subgroup analysis of the SMART cohort also suggested that patients not receiving chemotherapy may benefit from prophylactic radiotherapy in terms of reducing PTM incidence (2/46 (4%) vs 8/37 (22%) in the immediate and deferred radiotherapy groups respectively (p= 0.02)). This may reflect that systemic chemotherapy effectively targets residual tumour cells seeded at the site of previous pleural interventions, negating the need for prophylactic radiotherapy as well. It may also explain why some of the older studies, conducted before the use of pemetrexed based treatment regimens appeared to show prophylactic radiotherapy to be more effective.

The use of IPCs for fluid management of persistent pleural effusions has increased markedly since the early prophylactic radiotherapy studies. The SMART trial agreed with the non-randomised data suggesting delivering radiotherapy to these catheters was not associated with complications or device damage [28, 29]. However, the incidence of PTM was not reduced by delivering prophylactic radiotherapy to patients with IPCs, although the numbers were small.

The cohorts recruited to the aforementioned RCTs have only included a small proportion of patients who have large thoracotomy scars from surgical procedures, with 9 in the SMART trial and none in the Boutin, Bydder and O'Rourke trials. Agarwal et al retrospectively observed 5/21 patients who had a thoracotomy developed a PTM. Given the lack of proven efficacy of radical surgical treatments for mesothelioma [30], only small numbers of patients are currently undergoing thoracic surgery [31]. It could be argued however, that these patients with the largest scars potentially have the most to benefit from prophylactic radiotherapy but the current studies have not recruited sufficient patients in this group to quantify its potential benefit. Should more invasive surgical interventions be established in the future, this may warrant reconsideration.

Future trials

It is hoped that The PIT Trial, another large, UK based RCT aimed at assessing the benefit of prophylactic radiotherapy in MPM which is currently in follow up will help clarify the ongoing uncertainties relating to its use in these subgroups [10, 32-35]. This trial has recruited 374 patients over two years and is currently in follow up. It randomised patients to either 21 Gray in 3 fractions of prophylactic radiotherapy with a superiorly configured field to take into account skin movement around the scar or no radiotherapy. The primary endpoint is the occurrence of PTMs 6 months after randomisation but patients will be followed up for 2 years with regular telephone consultations.

Close liaison between the SMART and PIT trial teams has ensured the data from the 2 trials can be combined to allow for future meta-analysis.

Conclusion

The role of prophylactic irradiation of tracts in mesothelioma is a much debated subject area, with controversy about its efficacy spanning a number of decades. Based on the body of randomised evidence, there is no evidence to suggest prophylactic irradiation of tracts is effective in reducing PTM incidence if delivered to all-comers with mesothelioma after pleural interventions. Even if it were to be mildly efficacious if delivered quickly and accurately after a pleural intervention, the lack of any symptom or quality of life benefits from the SMART study, would suggest that in this would not confer any patient-centered benefit above careful clinical follow up. These patients have a limited lifespan with only palliative treatments available to them and hence these patient-focused outcomes are of paramount importance.

Further data is required to ascertain whether certain patient groups, such as those with epithelioid-only histology or those not undergoing chemotherapy stand to benefit from prophylactic radiotherapy and it is hoped the PIT study data will clarify this further.

Based on the available clinical trial data, we would not advocate the routine prophylactic irradiation of tracts in mesothelioma, but instead careful clinical follow up to ensure PTMs are identified and treated promptly to minimise symptoms.

Key points

- Prophylactic radiotherapy to prevent procedure tract metastases (PTMs) is a controversial topic with conflicting results from randomised controlled trials.
- Recent larger trials have not shown any evidence that routine use of prophylactic radiotherapy reduces incidence of PTMs.
- Certain subgroups of patients may benefit more from prophylactic radiotherapy, such as those with epithelioid disease not receiving systemic chemotherapy, and future studies may help to clarify best practice.

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