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Prophylactic irradiation meta-analysis in reducing procedure tract metastasis incidence in malignant pleural mesothelioma

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► *Review article*

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ABSTRACT

***Background*:** Malignant pleural mesothelioma (MPM) diagnoses are primarily based on pleural biopsy. Invasive procedures may result in iatrogenic dissemination of tumor cells along the subcutaneous channels. The purpose of our study was to clarify the effect of prophylactic radiotherapy on the incidence of metastasis in patients afflicted with MPM. ***Materials and Methods*:** Relevant studies were searched in PubMed, Cochrane Library, and Embase databases from the establishment of the library to February 2022. The quality of the included studies was evaluated, and the data were statistically analyzed. ***Results*:** Seven articles were obtained, and 1030 patients were included in the study, which allowed comparison of the procedure to track metastases (PTMs) incidences between radiotherapy and control groups. The results revealed statistically significant differences in the incidence of PTMs between the two groups (OR=0.48, 95% confidence interval [CI]:0.33, 0.69, p<0.0001). Subgroup analysis further showed that preventive radiotherapy could effectively reduce the incidence of PTMs in MPM patients who underwent large-caliber invasive procedures but could not reduce the incidence of PTMs after small-caliber invasive procedures. Prophylactic radiotherapy in patients with epithelial PTM types could reduce the incidence (OR=0.27, 95% CI:0.11, 0.69, P=0.006). ***Conclusion*:** Prophylactic radiotherapy is safe and can effectively prevent the occurrence of iatrogenic PTMs in patients with epithelial MPM who have undergone thoracotomy, thoracoscopy, indwelling chest wall drainage tubes, and other large-caliber operations.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a diffuse invasive tumor originating from the pleural mesothelial tissue with an average survival time of 8-14 months [1]. Asbestos exposure is a risk factor for morbidity [2]. MPM diagnosis is primarily based on pleural biopsy, and typical cases present with chest pain, dyspnea, and malignant pleural effusion; therefore, many patients undergo puncture diagnosis and pleural effusion management [3]. These invasive procedures may result in iatrogenic dissemination of tumor cells along the subcutaneous channels, causing procedure track metastases (PTMs). Metastasis of the operating channel leads to painful subcutaneous nodule or neoplastic skin ulcer formation, which has negative psychological and physiological consequences in patients with MPM [4,5]. A small-scale randomized controlled study (RCT) involving 40 patients with MPM proved that prophylactic irradiation of the puncture site could significantly reduce PTM incidence [6]. Since then, preventive radiotherapy after invasive manipulation of the pleura in patients with MPM has been widely used. However, many recent clinical studies have failed to demonstrate the effectiveness of preventive irradiation to reduce the incidence of PTMs.

A RCT published in 2019 reported no advantage in the use of PIT to prevent PTM. Later, it was suggested that this study was statistically flawed. Recommendations regarding the need for prophylactic radiotherapy vary among clinical practice guidelines in different regions [7-10]. The puncture site, techniques, field size, dose, and timing of prophylactic radiotherapy at the puncture site are controversial [11]. Here, a meta-analysis was used to conduct a comprehensive evaluation of existing RCTs and cohort studies to clarify the effect of preventive radiotherapy on the incidence of PTMs in patients with MPM.

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MATERIALS AND METHODS

Search strategy

Using the search terms "malignant pleural mesothelioma, prophylactic radiotherapy, prophylactic radiation", the PubMed, Cochrane Library, Web of Science, and EMBase databases were searched. Searches were conducted until February, 2022.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients diagnosed with MPM by pathological or cytological examination and underwent invasive diagnosis and treatment operations, regardless of age, sex, or race; (2) the experimental group patients received local prophylaxis for the puncture site. The radiotherapy scheme was not limited and the control group did not receive prophylactic radiotherapy at the puncture site; (3) the incidence of PTMs, occurrence time, pain, adverse reactions to prophylactic radiotherapy, survival time, quality of life, and other outcome indicators were reported and (4) the research type was RCT, cohort study, and the language was English.

The exclusion criteria were as follows: (1) studies with unclear outcome indicators and (2) duplicate publications.

Data extraction

Two researchers independently screened the literature and extracted the data according to the inclusion and exclusion criteria. The extracted data included: (1) general information, including title, author, publication time, etc.; (2) characteristics of trial design, including the basic conditions of the subjects, baseline comparability of each trial group, intervention measures, blinding, and allocation concealment; and (3) incidence of PTMs, adverse reactions (radiodermatitis, pain, and gastrointestinal reactions), and other outcome indicators. Disagreements were resolved by consultation or by a third investigator.

Evaluation of literature quality

The quality of the included RCTs was evaluated according to the risk bias assessment tool recommended by the Cochrane Collaboration, which was divided into three levels: "low, "high, and "uncertain. The risk of bias of the included cohort studies was assessed using the Newcastle-Ottawa Scale (NOS).

RESULTS

Basic characteristics of the included studies and literature quality evaluation

A total of 772 related studies were retrieved; 576 articles were obtained after eliminating duplicate literature via literature management software, 527 studies that did not meet the inclusion criteria, such as non-controlled studies and intervention measures, were excluded from reading titles and abstracts, and 49 studies were initially obtained. After reading the full text and excluding 41 papers that did not meet the inclusion criteria, 7 papers were finally obtained, with a total of 4 RCTs [6, 12-14], 3 cohort studies [15-17], and a total of 1030 patients. The literature screening process and the results are shown in figure 1. The general information on the included studies is presented in table 1. The risk of bias assessment of the included studies is presented in figure 2.

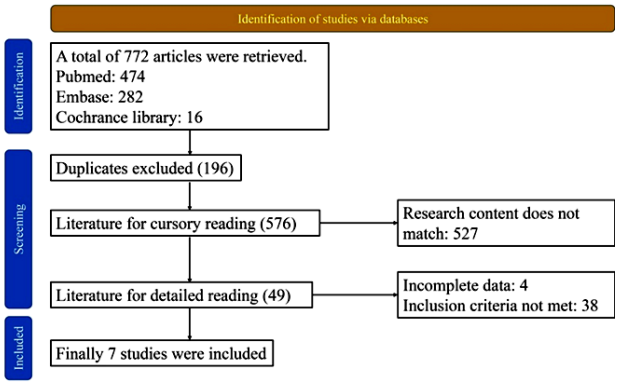


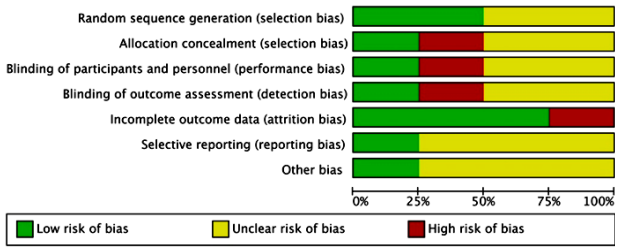
Figure 1. Flow chart of the literature search.

Table 1. Characteristics of included studies.

Study	Type	Samples	prophylactic radiation			
			Time	Program	Rays	Scope
Boutin 1995	RCT	40	10-15 days	21Gy/3F	12.5-15 MeV	16-100cm^2
O'Rourke 2007	RCT	61	<42 days	21Gy/3F	9MeV	6cm diameter
Clive 2016	RCT	203	<42 days	21Gy/3F	6-18MeV	7cm diameter
Bayman 2019	RCT	375	<42 days	21Gy/3F	NA	3cm diameter
Cellerin 2004	Cohort	58	37 days	NA	NA	NA
Chapman 2008	Cohort	122	52 days	21Gy/3F	NA	NA
Froment 2011	Cohort	171	27 days	21Gy/3F	6MV	63.5 cm^2

The effect size (OR) was used as the abscissa, and the reciprocal 1/SE (logOR) of the effect size to the standard error of the value was used as the ordinate

Figure 2. Risk of bias profile of the included studies.



Meta-analysis

PTM incidence

Seven studies with a total of 1030 patients compared the incidence of PTMs between the radiotherapy and control groups. Statistical

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heterogeneity was observed among the results of the included studies (I2=43%, p=0.10). The fixed effects model was used for meta-analysis and showed that there was a statistically significant difference in the incidence of PTMs between the two groups (OR=0.48, 95% CI).:0.33, 0.69, p<0.0001), suggesting that preventive radiotherapy had a significant effect on reducing the incidence of PTMs (figure 3).

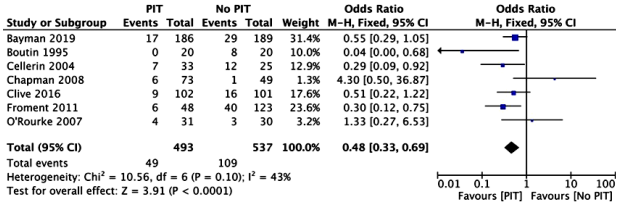

Figure 3. Procedure track metastases incidences.

PTM incidence in large-caliber invasive procedures

According to the literature, large- and small-caliber invasive procedures were defined. Large-caliber invasive procedures include thoracotomy, thoracoscopy, and the use of indwelling drainage tubes. Small-bore invasive procedures include fine-needle aspiration (fine needle aspiration), pleural biopsy (Abram needle), and cytology. Four studies reported the incidence of PTMs in radiotherapy and control groups of patients with MPM undergoing large-bore invasive procedures. There was no statistical heterogeneity among the results of the included studies (I2=18%, p=0.30), and the fixed-effect model analysis showed a statistically significant difference in the incidence of PTMs between the two groups (p=0.01), suggesting that preventive radiotherapy can effectively reduce the incidence of PTMs in patients with MPM undergoing large-caliber invasive procedures (figure 4).

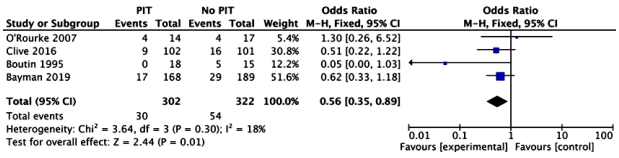

Figure 4. PTM incidence in large-caliber invasive procedures.

PTM incidence in small-caliber invasive procedures

Two studies reported the incidence in radiotherapy and control groups in patients with MPM undergoing small-bore invasive procedures. The difference in incidence was not statistically significant (OR=1.09, 95% CI:0.02, 49.30, P=0.97). However, considerable heterogeneity was observed among the studies. Hence, we suggest that preventive radiotherapy after small-bore pleural invasive surgery in patients cannot effectively reduce the incidence of PTMs (figure 5).

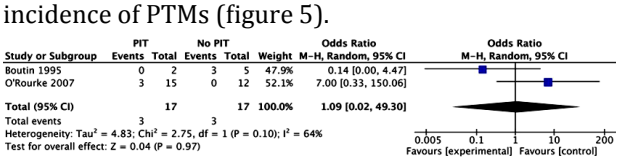

Figure 5. PTM incidence in small-bore invasive procedures.

PTM incidence in patients with pathological types of MPM

Two studies reported the associated pathological information. The analysis results indicated that preventive radiotherapy in patients with the epithelial PTM type could reduce the incidence (OR=0.27, 95% CI:0.11, 0.69, P=0.006). For patients in other pathological analyses, the difference in the incidence of PTMs was not statistically significant (OR=0.78, 95% CI:0.18, 3.38, P=0.74) (figure 6).

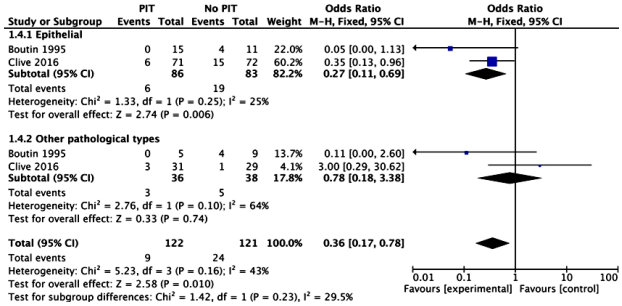

Figure 6. PTM incidences in different pathological types.

Funnel plot analysis

Publication bias funnel plot analysis was performed on the included studies, and revealed a symmetrical funnel plot, indicating no notable publication bias (figure 7).

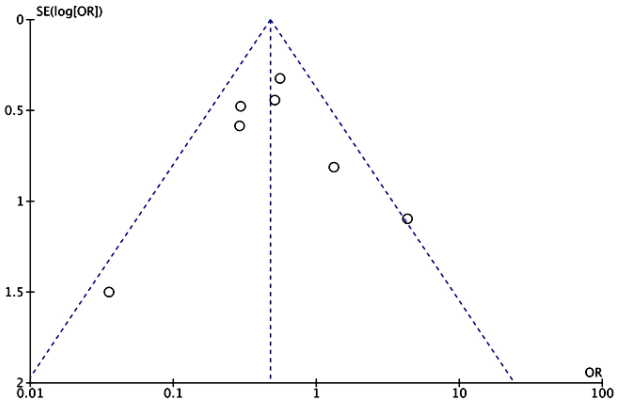

Figure 7. Bias funnel plot of the included studies.

DISCUSSION

MPM can manifest as extensive chest wall thickening and a nodular bulge on computed tomography (CT), and it is often difficult to distinguish from lesions such as tuberculous pleurisy. Recently, positron emission tomography (PET) combined with magnetic resonance imaging has greatly improved the sensitivity of MPM diagnosis and assists in local staging. However, due to the high price and limitations (such as false positives and negatives), MPM clinical diagnosis remains mainly reliant on invasive methods such as pleural pathology and immunohistochemistry [18]. MPM prognoses are generally very poor, and treatment for advanced patients is focused on reducing pleural effusion,

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relieving dyspnea, and improving the quality of life. The vast majority of MPM patients require invasive pleural procedures during diagnosis and treatment. When the iatrogenic operation destroys the original coverage pattern of the tumor, the tumor cells spread from the pleura to the subcutaneous tissue along the invasive operation channel or a few tumor cell clusters left in the operation channel recover the operation channel in the same way, forming PTMs [19].

The tumor then spreads and metastasizes along the surgical pathway, causing potential complications in patients with malignant pleural mesothelioma, with a metastasis incidence of approximately 20% [20]. These invasive nodules can penetrate the chest wall and may cause pain and nerve damage, seriously affecting the quality of life of patients; hence it is worthy to pursue preventive radiotherapy. The invasive channel metastasis incidence increases with an increase in operating diameter. The metastasis rates after pleural biopsy, thoracoscopic surgery, and thoracotomy are 10 %, 13%, and 26 %, respectively [20]. Boutin *et al.* (1995) were the first to report a small randomized controlled trial in which 40 patients with malignant pleural mesothelioma received prophylactic radiotherapy following invasive procedures to significantly reduce the incidence of metastases [6]. After radiotherapy, the local blood supply was reduced, which reduced the release of angiogenic and growth factors, thereby limiting the survival ability of tumor cells and ultimately reducing the occurrence of channel metastasis.

Different operations lead to different incidences of PTMs. Agarwal *et al.* (2006) retrospectively reported the incidence of PTMs in 100 patients with MPM using different procedures, in which small-bore puncture, thoracoscopy, and thoracotomy was performed in 4%, 16%, and 24%, respectively [21]. Furthermore, Thomas *et al.* (2014) reported 13.6% of PTMs in 66 MPM patients with indwelling chest wall drainage tubes [22]. *In-vitro* experiments revealed that mesothelioma cells are highly sensitive to radiation; however, due to the limitation of pulmonary radiation toxicity, radical hemithoracic radiotherapy is mostly performed after extrapleural pneumonectomy [23]. The preventive irradiation range is limited, and the dose is small, which is relatively safe and feasible in clinical practice. Prophylactic radiotherapy kills a small number of seeded cells before the formation of clonal clusters. Simultaneously, tissue fibrosis, decreased angiogenesis, and decreased oxygen supply after radiotherapy complicate the colonization of tumor cells in harsh conditions [2]. Currently, one review roughly combined the results of three RCTs and failed to determine the effectiveness of preventive radiotherapy [24]. Furthermore, the conclusions of trials on whether prophylactic radiotherapy can reduce the incidence of PTMs are inconsistent.

Our analysis showed that prophylactic radiotherapy did not reduce the incidence of PTMs in all patients with MPM. These results are inconsistent with previous research findings [11] and are not similar to the findings of Lee *et al.* (2021), which is also a meta-study [25]. The main reason for the different results is the expansion of the study sample. However, preventive radiotherapy can reduce the occurrence of iatrogenic PTMs in patients with MPM and epithelial-type MPM who undergo thoracotomy, thoracoscopy, indwelling chest wall drainage tubes, and other large-caliber operations. First, due to the larger operating caliber, the greater the probability of tumor cells spreading in the channel between the skin and pleura, the greater the number and the higher the true incidence of metastasis. Preventive irradiation can reduce local metastases, which is consistent with the findings of Clive *et al.* (2013) [8]. Second, there may be differences in radiosensitivity between the different pathological types of mesothelioma cells. *In-vitro* experiments have shown that the sensitivity of human mesothelioma cells to radiation is closely related to pathological subtypes. When the dose reaches 25 Gy, the epithelial cell line produces a large number of pro-inflammatory mediators, which further activate dendritic cells and induce an immune response to kill tumor cells.

However, this phenomenon was not observed in sarcoma subtype cell lines. Therefore, it is speculated that the currently widely used radiotherapy regimen fails to cause lethal damage to the sarcoma-type and mixed-type tumor cells. Finally, due to the low incidence of MPM, the included RCTs were mostly small sample trials, the heterogeneity between trials was large, the significant evidence was not enough to cover up the insignificant parts, and the overall pooling was not statistically significant, and some subgroups did not represent statistically significant results.

The included studies reported that the most recent adverse reactions related to prophylactic radiotherapy were mild radiodermatitis, pain, chest discomfort, vomiting, nausea, anorexia, and other gastrointestinal reactions. No long-term adverse reactions were noted. This shows that prophylactic irradiation is relatively safe and that complications can be tolerated. The radiation doses included in this meta-analysis were all 21 Gy/3 F, but there were still differences in the range of experimental designs and the initiation of radiation therapy. However, no experimental studies have been conducted on the optimal preventive radiation regimen.

The main limitations of this study are as follows: (1) the number of included studies was small, the sample size was small, the quality was low, and the number of studies for subgroup merging was small, which may have affected the authenticity of the conclusions of this study. (2) Only English literature was included, creating the possibility that literature in other languages were not included. (3) To expand the

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sample size, this study combined the results of RCTs and cohort studies simultaneously, which may create bias. (4) The main outcome index of all included studies was PTMs, regardless of whether they showed symptoms or not, and they were rarely confirmed by pathology - creating the possibility that scarring may have been mistaken for subcutaneous nodules formed by tumor metastasis. (5) There were differences in the radiotherapy regimens included in the studies, and the effectiveness of different radiotherapy regimens was not distinguished. (6) The included studies did not specify the physical status of the patients, and some patients could have received chemotherapy or supportive treatment simultaneously, which may have an impact on the incidence of PTMs.

CONCLUSION

Prophylactic radiotherapy is safe and can effectively prevent iatrogenic PTMs in patients with epithelial MPM who have undergone thoracotomy, thoracoscopy, indwelling chest wall drainage tubes, and other large-caliber operations.

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***Declaration of competing interest*:** The authors declare no competing interests.

***Author contributions*:** Pu-En Chen participated in the design of the study and performed the statistical analysis. Hua-Fei Chen, Chun-Wei Xu and Wen-Xian Wang conceived of the study, and participated in its design and Li-Chao Huang, Xiao-Feng Li, Gang Lan, Zhan-Qiang Zhai, You-Cai Zhu, Kai-Qi Du, Mei-Yu Fang coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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