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original report

Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial

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abstract

PURPOSE Prophylactic irradiation to the chest wall after diagnostic or therapeutic procedures in patients with malignant pleural mesothelioma (MPM) has been a widespread practice across Europe, although the efficacy of this treatment is uncertain. In this study, we aimed to determine the efficacy of prophylactic radiotherapy in reducing the incidence of chest wall metastases (CWM) after a procedure in MPM.

METHODS After undergoing a chest wall procedure, patients with MPM were randomly assigned to receive prophylactic radiotherapy (within 42 days of the procedure) or no radiotherapy. Open thoracotomies, needle biopsies, and indwelling pleural catheters were excluded. Prophylactic radiotherapy was delivered at a dose of 21 Gy in three fractions over three consecutive working days, using a single electron field adapted to maximize coverage of the tract from skin surface to pleura. The primary outcome was the incidence of CWM within 6 months from random assignment, assessed in the intention-to-treat population. Stratification factors included epithelioid histology and intention to give chemotherapy.

RESULTS Between July 30, 2012, and December 12, 2015, 375 patients were recruited from 54 centers and randomly assigned to receive prophylactic radiotherapy (n = 186) or no prophylactic radiotherapy (n = 189). Participants were well matched at baseline. No significant difference was seen in the incidence of CWM at 6 months between the prophylactic radiotherapy and no radiotherapy groups (no. [%]: 6 [3.2] *v* 10 [5.3], respectively; odds ratio, 0.60; 95% CI, 0.17 to 1.86; $P = .44$). Skin toxicity was the most common radiotherapy-related adverse event in the prophylactic radiotherapy group, with 96 patients (51.6%) receiving grade 1; 19 (10.2%), grade 2; and 1 (0.5%) grade 3 radiation dermatitis (Common Terminology Criteria for Adverse Events, version 4.0).

CONCLUSION There is no role for the routine use of prophylactic irradiation to chest wall procedure sites in patients with MPM.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Malignant pleural mesothelioma (MPM) is almost exclusively linked to asbestos exposure and has a latency period of 12 to 50 or more years.[1-3] Survival rates are gradually improving but remain poor, with 2-year survival ranging from 17% to 46%, according to clinical stage, in the United States.[4]

The diagnosis and treatment of MPM usually involves an invasive procedure at the chest wall, which can cause tumor-cell seeding at the site of the procedure and result in the development of a subcutaneous tumor. Studies have reported that the incidence of chest wall metastases (CWM) ranges from 2% to 50%.[5-13]

To minimize tumor seeding and prevent the development of CWM, it has been widespread practice for the last two decades to deliver prophylactic radiotherapy to the site of the chest wall procedure,[14,15] although the efficacy of this approach is uncertain and based on conflicting data from underpowered clinical trials conducted before the era of chemotherapy.[16-20] This has resulted in conflicting recommendations in international guidelines and consensus that suitably powered randomized trials are needed.[21-24] In the current trial, the aim was to determine whether prophylactic radiotherapy after a chest wall procedure reduces the incidence of CWM.

METHODS

Study Design

This multicenter, open-label, phase III, randomized controlled trial recruited patients from 54 hospitals across the United Kingdom. Participants gave written informed consent and the study was performed according to the Declaration of Helsinki and Good

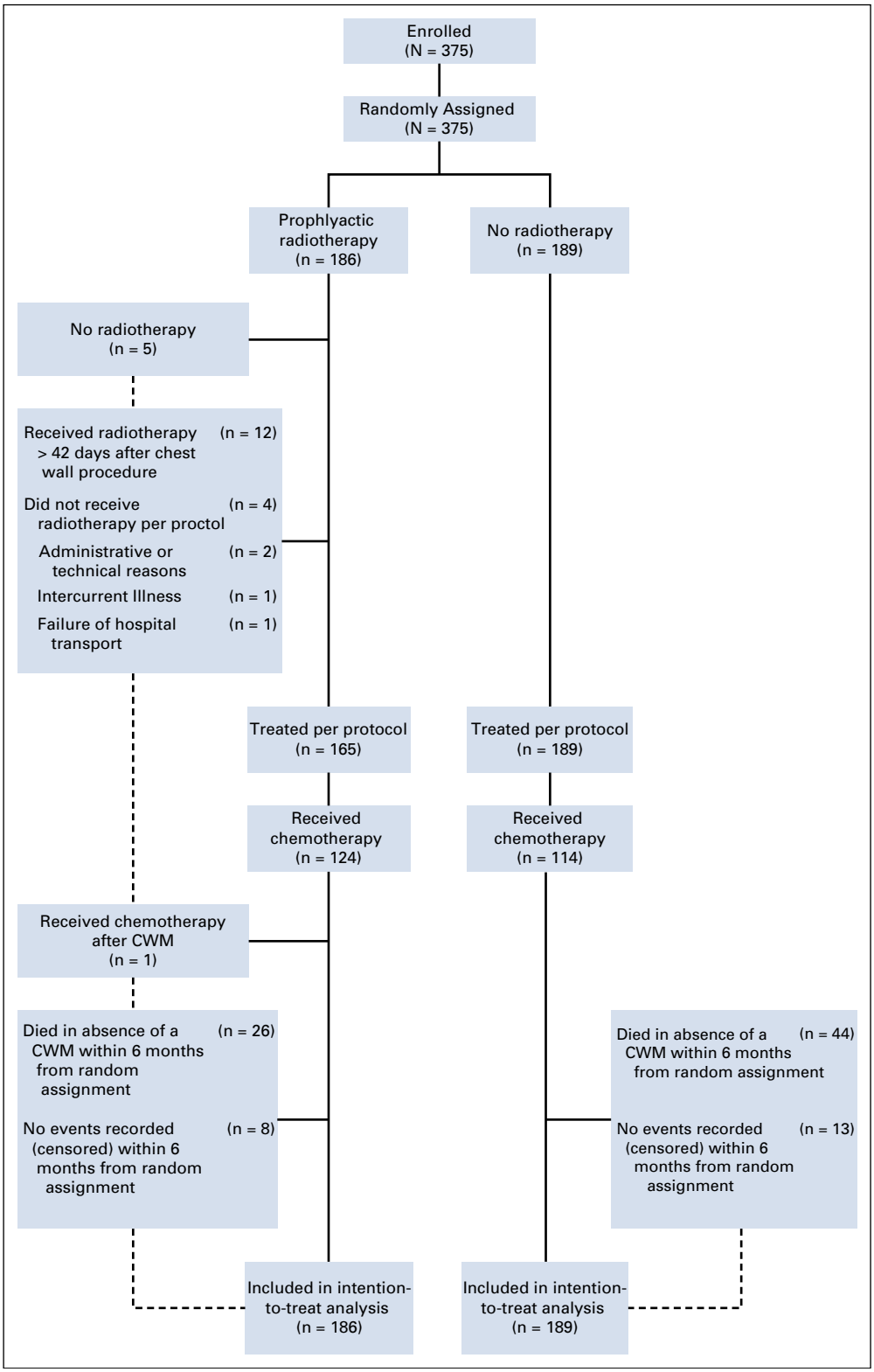

FIG 1. Trial profile. CWM, chest wall metastases.

Clinical Practice Guidelines. The trial and subsequent protocol amendments were approved by the Greater Manchester West Ethics Committee of the UK National Research Ethics Service (12/NW/0249). The full protocol was published before the completion of trial follow-up.[25]

Participants

Eligible patients were aged 18 years or older; had a diagnosis of MPM confirmed by a thoracic malignancy multidisciplinary team; had inoperable disease or were medically unsuitable for surgery; had an Eastern

TABLE 1. Baseline Characteristics

Characteristic	No RT (n = 189)	Prophylactic RT (n = 186)
Age (range), years	74.6 (49.2-90.4)	72.9 (52.3-89.8)
Sex		
Male	167 (88.4)	167 (89.8)
Female	22 (11.6)	19 (10.2)
Procedure		
VATS	97 (51.3)	108 (58.1)
Local anesthetic thoracoscopy	51 (27.0)	50 (26.9)
Intercostal chest drain	16 (8.5)	11 (5.9)
Open surgical biopsy	10 (5.3)	5 (2.7)
Other	15 (7.9)	12 (6.5)
ECOG PS score		
0	45 (23.8)	60 (32.2)
1	106 (56.1)	105 (56.5)
2	38 (20.1)	21 (11.3)
Histology		
Epithelioid	140 (74.1)	148 (79.6)
Other	49 (25.9)	38 (20.4)
Intention to administer chemotherapy		
Yes	135 (71.4)	133 (71.5)
No	54 (28.6)	53 (28.5)

NOTE. Data reported as No. (%) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; RT, radiotherapy; VATS, video-assisted thoracoscopic surgery.

Cooperative Oncology Group performance status score of 0 to 2; had undergone a chest wall procedure, including open surgical biopsy, video-assisted thoracoscopic surgery biopsy, local anesthetic thoracoscopy, or insertion of a chest drain; had a chest wall procedure scar visible at time of random assignment; and were able to start prophylactic radiotherapy within 42-days of the chest wall procedure.

Patients were ineligible if they had an open thoracotomy (the resulting large scar or tract would not be adequately covered with the electron field arrangement used) or had undergone a needle biopsy (the resulting scar would not be visible at the time of random assignment), had received previous thoracic radiotherapy to the region of the chest wall procedure site, were currently receiving chemotherapy, or had an indwelling pleural catheter in situ at the chest wall procedure site.

Randomization and Masking

Patients were randomly assigned on 1:1 to receive either prophylactic radiotherapy or observation. A variant of an adaptive, biased-coin randomization method was used to favor balanced allocations in the four strata formed from epithelioid histology (no/yes) and intention to give chemotherapy (no/yes). Allocations were to the lower recruiting arm within a stratum with probability 0.5 if the imbalance was within a predefined limit (3 for no intention and 6 for intention to give chemotherapy) and 0.75 otherwise. Randomization was undertaken centrally using a bespoke randomization computer system. Patients and clinicians were not masked to treatment allocation.

Procedures

A detailed account of the procedure is given in the published full protocol.[25] Patients randomly assigned to the prophylactic radiotherapy group started prophylactic radiotherapy within 42 days of the most recent chest wall procedure. Radiotherapy was delivered using a single electron field at a dose of 21 Gy in three fractions, once per day over three consecutive working days.

The radiotherapy target volume comprised the procedure scar with a 3-cm margin inferiorly and laterally. The superior margin corresponded to the superior border of three ribs superior to the procedure scar. This approach maximized the chance of the whole procedure tract, from skin to pleura, being covered by the treatment field, which commonly runs over the rib superior to the site of insertion on the chest wall. The electron energy was determined

TABLE 2. Logistic Regression Analysis of Primary Outcome: Chest Wall Metastases Within 6 months (29 weeks) From Randomization

Term	OR	95% CI	*P*
Trial arm*	0.598	0.212 to 1.684	.33
Confirmed epithelioid histology†	0.949	0.296 to 3.039	.93
Intention to give chemotherapy†	1.204	0.378 to 3.834	.75
Constant	0.051	0.012 to 0.206	< .001

Abbreviation: OR, odds ratio.
*0 = No radiotherapy; 1 = prophylactic radiotherapy.
†0 = No; 1 = yes.

according to local electron dose-depth calculations ensuring greater than 90% of the prescribed dose was delivered to the pleura and to the skin surface, facilitated by applying a 5-mm tissue-equivalent bolus to the whole treatment field, if required.

Chemotherapy was initiated at least 1 week after radiotherapy for patients in the prophylactic radiotherapy group, and after randomization for patients in the control group, at the discretion of the treating clinician. Patients were followed up monthly for 24 months or until the development of CWM or death. Patients were reviewed in clinic at the time of random assignment, and at 6, 12, 26, and 52 weeks after randomization for an examination of the chest wall to assess for visible and/or palpable signs of CWM and for toxicity assessment, using Common Terminology Criteria for Adverse Events, version 4.0. In addition, patients received a monthly telephone follow-up with a research nurse to determine if they had noted any chest wall nodules. If a patient was suspicious that a nodule had developed, they were invited to the clinic for assessment.

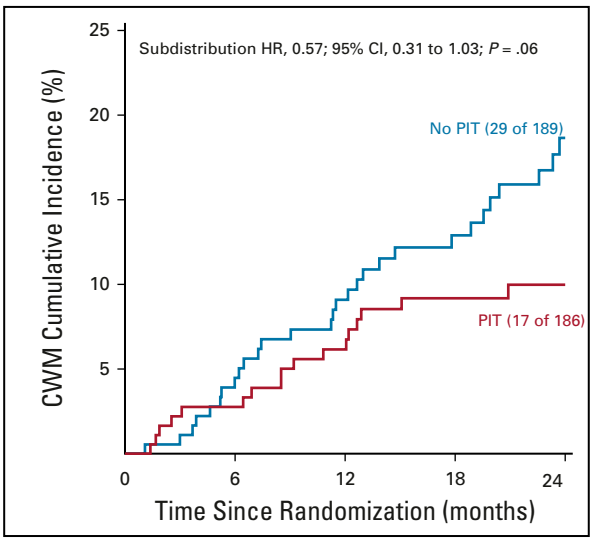

FIG 2. Cumulative incidence of CWM in the prophylactic radiotherapy group and the no radiotherapy group. CWM, chest wall metastases; HR, hazard ratio; PIT, prophylactic irradiation of tracts.

Patients were asked to complete a visual analog scale (VAS) to score for pain (on a scale of 0 to 100 mm, with no pain at 0 mm and worst possible pain at 100 mm) at the time of randomization, and at each telephone and clinic follow-up. Patients were specifically asked to only consider pain at the original site of the chest wall procedure or at the site of the chest wall nodule, if present. Patients were removed from the study only if they withdrew consent for ongoing trial follow-up.

Outcomes

The primary end point was the incidence of metastases on the ipsilateral chest wall 6 months (29 weeks to allow for some variation in follow-up appointments) from randomization, within the intention-to-treat population. Incidence of ipsilateral CWM was considered a clinically relevant and reproducible primary end point not reliant on observer interpretation of a virtual radiotherapy field, which was particularly important for patients in the no-radiotherapy arm who did not have a radiotherapy field planned at baseline. The date of CWM was recorded as the date CWM was confirmed by the investigator in clinic. If the patient was unable to attend the outpatient clinic, then the date of CWM was recorded as the date of the telephone consultation when the metastasis was reported.

Predefined secondary outcomes were incidence of ipsilateral CWM 12 months from randomization; time from randomization to ipsilateral CWM; position of ipsilateral CWM in relation to the radiotherapy field in patients randomly assigned to the prophylactic radiotherapy group (in field/out of field); acute and late skin radiotherapy toxicity (Common Terminology Criteria for Adverse Events, version 4.0); pain from ipsilateral CWM (VAS score).

Statistical Analysis

The sample size calculation was based on the published literature,[5-13] with the crude rate of CWM after a chest wall procedure expected to be 15%, occurring 80% to 90% of the time within 6 months of the chest wall procedure. Comparing the proportion of patients in whom CWM developed by 6 months and the proportion of patients in whom CWM did not develop or the proportion dying without CWM within 6 months, it was considered that a reduction in the incidence from 15% to 5% in favor of prophylactic radiotherapy would be clinically significant. On the basis of a two-arm trial with a 5% significance level, two-sided test, and 80% power, 280 patients would be required. It was anticipated that 25% of patients would not survive for 6 months after random assignment; therefore, an additional 94 patients were required, for a total of 374 patients. The study was powered to address the primary outcome only, not the secondary end points. Before analysis, it was recognized that it would be more appropriate to include patients not surviving 6 months in the denominator rather than excluding them, because the estimates from the

TABLE 3. Fine and Gray Regression Model for the Cumulative Incidence of Chest Wall Metastases With the Competing Risk of Death Without Preceding Chest Wall Metastases

Term	Subdistribution HR	95% CI	*P*
Trial arm*	0.574	0.310 to 1.063	.08
Confirmed epithelioid histology†	0.859	0.433 to 1.703	.66
Intention to give chemotherapy†	1.093	0.567 to 2.107	.79

Abbreviation: HR, hazard ratio.
*0 = No radiotherapy; 1 = prophylactic radiotherapy.
†0 = No; 1 = yes.

binary analysis would then be more in line with those from a competing risks analysis.

A Fisher's exact test was used to compare the cumulative incidence of CWM between the two arms at 6 months. A logistic regression analysis was also conducted that adjusted for the two stratification factors, histologic subtype, and intention to give chemotherapy, used in the randomization algorithm.

Time from randomization to CWM was compared using a Fine and Gray competing risks regression model accounting for the competing risk of death without CWM. Based on the hypothesis that CWM cause pain and result in an increase in VAS pain score by at least 20 points, a VAS pain score recorded after development of a metastasis was compared with the baseline score and the differences compared using a Wilcoxon matched-pairs test. Toxicity and position of CWM in relation to the radiotherapy field in patients randomly assigned to the prophylactic radiotherapy group were reported descriptively. The statistical package used for the analyses was Stata, version 13.1; and R. This study was registered with International Standard Registered Clinical Trial Number (ISRCTN 04240319).

RESULTS

Between July 30, 2012, and December 12, 2015, 375 patients were recruited from 54 centers and randomly assigned to receive prophylactic radiotherapy (n = 186) or no prophylactic radiotherapy (n = 189; Fig 1). Baseline characteristics of the two groups were well balanced (Table 1), although there was a greater proportion of patients with Eastern Cooperative Oncology Group performance status score of 2 in the no-radiotherapy group (20.1%) compared with the prophylactic radiotherapy group (11.3%). The proportion of patients receiving chemotherapy was well balanced between the two groups (66.7% in the prophylactic radiotherapy group compared with 60.3% in the no-radiotherapy group). Median time from randomization to first cycle of chemotherapy was 25 (range, 6 to 210) days in the prophylactic radiotherapy group compared with 17 (range, 2 to 400) days in the no-radiotherapy group. In both groups, greater than 90% of patients receiving chemotherapy were treated with a pemetrexed and platinum doublet. Of the 186 participants allocated to the prophylactic radiotherapy group, 165 received a single radiotherapy field delivering 21 Gy in three fractions, and 16 participants had two chest wall procedure sites treated, each receiving 21 Gy in three fractions.

TABLE 4. Change in VAS Pain Score at Development of Chest Wall Metastases, Compared With Baseline

Change in VAS Pain Score	Radiotherapy	No Radiotherapy	Total (%)
No change/decrease	8	12	20 (52.6)
Increase	7	11	18 (47.4)

Abbreviation: VAS, Visual Analog Scale.

At the time of analysis, the proportion of CWM 6 months after randomization was 3.2% (six of 186 patients) versus 5.3% (10 of 189 patients) in the prophylactic radiotherapy group and the no-radiotherapy group, respectively (odds ratio [OR], 0.60; 95% CI, 0.17 to 1.86; $P = .44$). Of the 375 censored cases, 21 (5.3%) were included in the analysis of proportions, but this did not markedly affect tests or estimates (Fisher's exact test, $P = .44$; χ^2 test, $P = .32$; and a test using point estimates and variances from the cumulative incidence curves, $P = .29$).

Logistic regression results adjusting for stratification factors for the primary analysis are listed in Table 2. The proportion of CWM 12 months after randomization was 8.1% (15 of 186 patients) versus 10.1% (19 of 189 patients), respectively (OR, 0.79; 95% CI, 0.36 to 1.69; $P = .59$).

There were 46 recorded CWM in total, 17 of 186 patients in the prophylactic radiotherapy group and 29 of 189 patients in the no-radiotherapy group. There was no significant difference in the cumulative incidence of CWM in the prophylactic radiotherapy group versus the no-radiotherapy group (subdistribution hazard ratio, 0.57; 95% CI, 0.31 to 1.03; $P = .06$), as shown in Figure 2. Similarly, there was no significant difference in cumulative incidence of CWM when controlling for the stratification factors (epithelioid histology [no/yes] and intention to give chemotherapy [no/yes]; Table 3).

In the prophylactic radiotherapy group, of the 17 participants in whom CWM developed, they developed within the prophylactic radiotherapy field in eight patients (47%), outside of the prophylactic radiotherapy field in seven (41%), and data were not recorded for two patients.

Of the 46 patients in whom CWM developed, 38 had their VAS pain score recorded at time of randomization and time of event (Table 4). After CWM developed, pain was scored as the same or better than baseline in 20 patients (52.6%) and worse in 18 of the 38 patients (47.4%), with 12 recording at least a 20-point increase in VAS pain score (Wilcoxon matched-pairs test, $P < .01$).

Skin toxicity was the most common radiotherapy-related adverse event in the 186 patients allocated to the prophylactic radiotherapy group. Radiation dermatitis grade 1 was reported in 96 (51.6%), grade 2 in 19 (10.2%), and

TABLE 5. Toxicity

	CTCAE Toxicity Grade					
	Prophylactic RT (n = 186)			No RT (n = 189)		
Adverse Event	1	2	3	1	2	3
Radiation dermatitis	96 (51.6)	19 (10.2)	1 (0.5)	0	1 (0.5)	0
Skin atrophy	6 (3.2)	0	0	1 (0.5)	0	0
Skin induration	13 (7.0)	1 (0.5)	0	7 (3.7)	0	1 (0.5)
Skin ulceration	2 (1.1)	0	0	0	0	0
Chest wall pain	37 (19.9)	17 (9.1)	5 (2.7)	31 (16.4)	13 (6.9)	2 (1.1)
Avascular necrosis	1 (0.5)	0	0	0	0	0
Rib fracture	0	1 (0.5)	0	0	0	0
Dermatologic radiation recall reaction	10 (5.4)	3 (1.6)	0	0	0	0
Pneumonitis	1 (0.5)	0	0	0	0	0

NOTE. Toxicity was graded according to CTCAE, version 4.0, maximum reported grade. Data reported as no. (%).
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; RT, radiotherapy.

grade 3 in 1 (0.5%) patient. One patient in the no-radiotherapy group recorded a grade 2 radiation dermatitis. This patient was treated with palliative radiotherapy after CWM developed. Radiation recall reaction was recorded after chemotherapy for 13 patients in the prophylactic radiotherapy group (10 [5.4%] grade 1, three [1.6%] grade 2). A rib fracture (grade 2) was recorded in one patient in the prophylactic radiotherapy group. Other adverse events of grade 3 or higher that were recorded were chest pain (five of 186 patients [2.7%] in the prophylactic radiotherapy group and two of 189 [1.1%] in the control group), and one reported grade 3 skin induration in the no-radiotherapy group (Table 5).

DISCUSSION

The results from this trial show that prophylactic radiotherapy to the site of a diagnostic or therapeutic chest wall procedure does not significantly reduce the incidence of subsequent CWM in patients diagnosed with MPM.

The incidence of CWM in the no-radiotherapy group was less than anticipated. The predicted incidence of CWM in the no-radiotherapy group of 15% at 6 months was based on historical clinical trials and case-series data.[5-13,16-18] The overestimation could reflect the impact of chemotherapy using pemetrexed and cisplatin or carboplatin, which has been shown to improve survival in patients with MPM,[26] and was planned at the time of randomization for greater than 70% of participants. The statistics for our study were based on previous clinical trials and case series conducted before palliative chemotherapy for MPM was an established practice.

The results of this study are consistent with the findings from the recently published Surgery for Mesothelioma After Radiation Therapy (SMART) trial,[27] a multicenter, phase III trial in which 203 patients were randomly assigned (1:1) to immediate radiotherapy to chest wall procedure sites or to deferred radiotherapy. The differences in participants recruited, radiotherapy technique, and end points between our trial and the SMART trial are shown in Table 6. No statistically significant difference was identified in the incidence of CWM at 12 months from randomization of the immediate and deferred radiotherapy groups (nine of 102 patients [8.8%] *v* 16 of 101 (15.8%), respectively; OR, 0.51; 95% CI, 0.19 to 1.32; $P = .14$). Prophylactic radiotherapy compared with deferred radiotherapy demonstrated no significant effect on quality of life, nor was there any discernible decrease in health care costs.[28] In contrast, an earlier study by Boutin et al[16] (N = 40 patients) demonstrated a significant reduction in the incidence of CWM in the prophylactic radiotherapy arm. In that study, conducted in the prechemotherapy era, the incidence of metastatic nodules in the no-radiotherapy group was high (40%). However, this hypothesis is not supported by two other similar randomized clinical trials conducted before the era of chemotherapy and that demonstrated a lower incidence of CWM in the no-radiotherapy compared with the prophylactic radiotherapy groups.[17,18]

The cumulative incidence analysis did not demonstrate a significant difference between the two groups in the time to CWM development. The divergence in the curves seen after 12 months from randomization illustrates that there were an additional 10 CWM in the no-radiotherapy group occurring later than 12 months after randomization, compared with only two in the prophylactic radiotherapy group. This difference in rate of CWM between the two groups after 12 months from randomization was higher in the group of participants with a histologic subtype known to be associated with a better prognosis (epithelioid histology) and for whom chemotherapy treatment was intended. This was an exploratory analysis, and the trial was not powered to detect a difference in the rate of CWM in these

TABLE 6. Comparison of PIT and SMART Trial Protocols

Characteristic	PIT	SMART
Sample size	374	203
Inclusion criteria		
Open thoracotomy	No	Yes
Thoracoscopy	Yes	Yes
Large-bore chest tubes (≥ 20 F)	Yes	Yes
Small-bore chest tubes (< 20 F)	Yes	No
Indwelling pleural catheters	No	Yes
Needle biopsy	No	No
RT field size	3-cm Lateral/inferior borders; variable superior border	2 cm all directions
RT dose/fractionation	21 Gy in three fractions over 3 days	21 Gy in three fractions over 3 days
Primary end point	Incidence of ipsilateral CWM at 6 months	Incidence of CWM within 7 cm of the margins of the procedure site at 12 months
Secondary end points	Time to CWM	Time to CWM
	Pain from CWM	Pain from CWM
	Toxicity of treatment	Toxicity of treatment
	Locality of metastases to RT field	Quality of life
		Incidence of CWM with indwelling catheters
		Effect of chemotherapy
		Semistructured qualitative interviews
		Health economic analysis
Follow-up	Clinic at 1, 3, 6, and 12 months; monthly telephone follow-up	Clinic at 1, 3, 6, 9, and 12 months; monthly telephone follow-up

Abbreviations: CWM, chest wall metastases; PIT, Prophylactic Irradiation of Tracts; RT, radiotherapy; SMART, Surgery for Mesothelioma After Radiation Therapy.

subgroups. It could be hypothesized that chemotherapy for MPM delays the development of CWM after a diagnostic or therapeutic procedure, resulting in a deferred benefit from prophylactic radiotherapy, particularly in patients with favorable histologic subtypes. This is consistent with findings of the SMART trial, which demonstrated a longer median time to development of CWM in patients with epithelioid subtype compared with other tumor subtypes and in patients who received chemotherapy compared with no chemotherapy.[27]

The current trial is larger than the four previous randomized, phase III clinical trials in this setting.[16-18,26] By using a variable radiotherapy field margin, it is, to our knowledge, the first trial to adequately cover the entire portal tract and account for the commonly used technique whereby the pleura is accessed by passing a device over the superior border of the adjacent rib to reduce the risk of injuring the intercostal neurovascular bundle, which runs along the inferior side of the rib.[29] Contrary to a commonly held belief that CWM are painful, this study demonstrated that more than half of the CWM analyzed did not result in an increase in VAS pain score.

This trial was limited by an absence of blinding of the participants and investigators. In addition, it could be argued that this trial was underpowered to detect a more modest reduction in the incidence of CWM after prophylactic radiotherapy than was predicted, in the era of palliative chemotherapy. However, the power of this study was based on a hypothesis considered clinically relevant. It is questionable whether a smaller benefit, and thus a larger number needed to treat, would be clinically relevant in this group of patients with a 1-year survival rate of less than 50%. Furthermore, the only previous randomized trial to have demonstrated a benefit from prophylactic radiotherapy in this setting delivered the first fraction of treatment within 15 days of a chest wall procedure, so the window of up to 42-days could explain the conflicting results. However, the study was designed to be pragmatic and translatable to the routine clinical setting, where 42 days is achievable but few patients are able to start treatment within 15 days of a diagnostic procedure.

In conclusion, the results of this study do not support the routine use of prophylactic radiotherapy after a diagnostic or therapeutic chest wall procedure in the era of

chemotherapy for patients diagnosed with MPM. Our findings confirm that prophylactic radiotherapy should not be considered part of the routine treatment of patients with MPM who can be spared the limited but common skin toxicity and the inconvenience of extra hospital visits conferred by this unnecessary practice.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.01678.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prophylactic Irradiation of Tracts in Patients With Malignant Pleural Mesothelioma: An Open-Label, Multicenter, Phase III Randomized Trial

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