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

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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] vs 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.
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

FIG 1. Trial profile. CWM, chest wall metastases.
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. 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 2Gy 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 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.
with the crude rate of CWM after a chest wall treatment.

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, 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.

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.

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; x² 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...
The (N = 40 patients) dem-

Toxicity (SMART) trial, from the recently published Surgery for Mesothelioma After

been shown to improve survival in patients with MPM, using pemetrexed and cisplatin or carboplatin, which has overestimation could re

on historical clinical trials and case-series data. The incidence of CWM in the no-radiotherapy group was 15% at 6 months was based

overestimation in patients diagnosed with MPM. The results from this trial show that prophylactic radio-

the no-radiotherapy group of 15% at 6 months was based on historical clinical trials and case-series data. 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 radio-

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 illustrates that there was an exploratory analysis, and the trial was not powered to detect a difference in the rate of CWM in these groups after 12 months from randomization was higher in

grade 3 in 1 (0.5%) patient. One patient in the no-

radiotherapy group recorded a grade 2 radiation dermadi-
tis. 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 radio-

therapy 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. The overestimation in patients diagnosed with MPM. The results from this trial show that prophylactic radio-

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 illustrates that there was an exploratory analysis, and the trial was not powered to detect a difference in the rate of CWM in these.

| Adverse Event                      | CTCAE Toxicity Grade | Prophylactic RT (n = 186) | No RT (n = 189) |
|-----------------------------------|----------------------|---------------------------|-----------------|
|                                   | 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 rea| 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.
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.

The current trial is larger than the four previous randomized, phase III clinical trials in this setting. 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. 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 palliative chemotherapy.
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

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

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