Needle-track metastases and prophylactic radiotherapy for mesothelioma

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Summary
Background: Mesothelioma invades the tracts made by chest instrumentation. Prophylactic radiotherapy is effective at preventing malignant seeding at these sites.

Methods: We assessed the use and effectiveness of radiotherapy at our centre in 39 of the 40 patients identified with mesothelioma between January 2000 and September 2003.

Results: Thirty-seven (95%) patients received radiotherapy to their chest instrumentation site between 6 and 42 days (median 26 days) following the diagnosis of mesothelioma. The radiotherapy field size varied, from 4 cm square to 14 × 10.5 cm. The radiotherapy was given as 21 Gy in 3 fractions over 1 week. In 3 patients (8%), there was already tumour invasion of the skin at the time of radiotherapy. In 2 other patients (5%), there was tumour recurrence following radiotherapy; in both this was at the edge of the previous radiotherapy fields. Further treatment was administered to an adjacent field in both. One patient with an indwelling pleural catheter developed tumour growth at the catheter insertion site. This was treated successfully with radiotherapy, with no catheter damage.

Conclusions: Prompt radiotherapy referral and radiotherapy field selection is important to maximise the effect of radiotherapy given to prevent chest wall tumour growth. There was no tumour growth in areas that were treated with radiotherapy. Further chest interventions outside the radiotherapy field should be followed with further radiotherapy.

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**Introduction**

Mesothelioma is a common malignant pleural tumour, with an incidence predicted to rise until 2015–2020. Its growth pattern is usually by local invasion, with metastases being a late phenomenon. It therefore invades the tracks made by chest instrumentation, including pleural aspiration, biopsy, chest drain and thoracoscopy. Prophylactic radiotherapy has been found to be effective at preventing malignant seeding at these sites in two studies, one a randomised controlled trial, where a 40% control group tumour rate was reduced to zero in the radiotherapy group. A delay in radiotherapy of more than 2 months was found to be associated with increased chest wall recurrence in a non-randomised study. On the basis of this data, management guidelines recommend prophylactic radiotherapy within 4 weeks following any invasive procedures. Although this treatment is clearly successful in clinical trials, it is important to know how trial results compare to clinical practice. There has been no previous description of needle tract metastases, their location and their relation to the previous radiotherapy field. Therefore, we report a review of a cohort of patients with mesothelioma, to assess the efficacy of prophylactic chest wall radiotherapy in a "real world" setting.

**Methods**

We performed a retrospective review of the notes of a cohort of patients with histopathologically confirmed malignant pleural mesothelioma, receiving radiotherapy for prophylaxis against tumour invasion into pleural instrumentation sites. All patients presenting to the Oxford pleural clinic with malignant mesothelioma between January 2000 and September 2003 were included in the study. Follow-up was until death or to at least 6 months after radiotherapy, to confirm an appropriate clinical course. The prophylactic radiotherapy was given with direct fields to an applied dose of 21 Gy in 3 fractions over 1 week as an out-patient (see Table 1). Radiotherapy was performed with electrons (10 MeV) or 6 MV photons with 1 cm chest wall bolus or 200 kV photons without chest wall bolus, if electrons unavailable, or do not cover target volume adequately. Radiotherapy field sizes used were based on the current radiotherapy guidelines at our centre, which suggest allowing a 2–2.5 cm margin for a needle biopsy and a 3–4 cm margin for a chest drain, aiming to encompass any track made from the skin to the pleura. The distance from the skin to the pleura is obtained from the computerised tomography (CT) scan (Fig. 1).

**Results**

Forty patients who fulfilled the entry criteria with mesothelioma were identified (see flow chart). The clinical notes were missing for one patient, generating available data for 39 (98% of subjects). The histological diagnosis of mesothelioma was made following thoracoscopy in 24 patients (62%); in others it was made from pleural fluid, tumour or lymph node examination. Epithelioid mesothelioma accounted for 44%, sarcomatoid 13%, biphasic 5% and the remaining 38% were mesothelioma of unspecified type.
Thirty-seven (95%) patients received radiotherapy to their chest procedure site. This began a median of 26 days (range 6–43 days) following referral after the histological diagnosis of mesothelioma. The other 2 patients (5%) from the cohort died rapidly after their diagnosis and did not therefore receive radiotherapy. Radiotherapy field sizes varied in size from 4 cm² to 14 × 10.5 cm, depending on whether one or multiple biopsy sites were being irradiated, and whether a chest drain had been inserted. The radiotherapy was well tolerated, with few adverse effects, although most patients described mild tiredness.

In 3 patients (8%) of the cohort, there was already tumour invasion of the skin and chest wall at the chest instrumentation site at the time of radiotherapy (20, 27 and 38 days after diagnosis). Two other patients (5%) developed chest wall tumour following radiotherapy. One of these had been treated with a large initial radiotherapy field (10 × 7.5 cm) to encompass chest procedure sites, and had further radiotherapy to a different field 3 months later, following further pleural aspirations. However, he developed tumour presumed to be at an unmarked aspiration site at the edge of one of the previous fields 12 months after his initial radiotherapy. The other patient had been treated initially with 2 adjacent fields (10 × 5 cm and 4 cm²), but relapsed after 6 months with a nodule at the edge of one of the previously treated fields. Both patients received further radiotherapy to a field adjacent to, but not overlapping, the previous field, at a dose of either 21 or 24 Gy in 3 fractions over 1 week. In all the other patients, there was no tumour growth within areas that had been treated with prophylactic radiotherapy. A Kaplan–Meier survival analysis was performed to define radiotherapy field relapse rate over time: at 6 months, the proportion surviving without radiotherapy field relapse was 0.96; at 12 months, the proportion surviving without radiotherapy field relapse was 0.96; at 24 months, the proportion surviving without radiotherapy field relapse was 0.9.

Out radiotherapy field relapse was 0.9 and at 48 months, the proportion surviving without radiotherapy field relapse was 0.9.

Six patients (15%) of the cohort had indwelling catheters (Denver Pleurx, CLS Medical) inserted for persistent pleural fluid and trapped lung. These patients did not receive prophylactic radiotherapy whilst the catheter was indwelling. One patient developed painful tumour growth from the chest insertion site into the pleural cavity to the catheter exit site, whilst the catheter was in situ, 6 months after its insertion. He received radiotherapy (30 Gy in 6 fractions) to a field encompassing the drain insertion point, whilst the catheter remained in situ, with no adverse effect on the catheter. There was some shrinkage of the tumour following radiotherapy. However 7 months later, further subcutaneous nodules developed on top of the tumour which had previously been irradiated. No further radiotherapy was given to this site.

Follow up of patients with mesothelioma following radiotherapy was at regular intervals by the physicians in the specialist pleural disease clinic. They were able to correlate symptoms of chest wall discomfort with the clinical disease progression and observe sites of chest wall irradiation for possible tumour growth. Patient survival was a median of 11 months following needle track radiotherapy (range 1 month–still alive at 57 months).

**Discussion**

Our cohort compares in size favourably to those used in previous published works (Boutin: 40
patients,\textsuperscript{2} Low: 20 patients over 4 years,\textsuperscript{3} de Graaf-Strukowska: 189 patients over 17 years\textsuperscript{4}). As 8% of our patients had developed tumour invasion by the time of radiotherapy, the need for prompt radiotherapy referral and early treatment following chest instrumentation in all patients is highlighted. The aim of our department is to commence irradiation within 2 weeks of chest instrumentation, but current practice is somewhat slower than this. There were two episodes of track site invasion following radiotherapy: one at a presumed unrecognised procedure site at the edge of the initial radiotherapy treatment field and one at the edge of the radiotherapy field. This was much lower than the control frequency of this problem in clinical trials.\textsuperscript{2} The edge of a radiotherapy field receives a lower radiation dose than the centre of the field and had the procedure site been marked, the original radiotherapy field could have been increased in order to encompass it. This emphasises that field selection is crucial to encompass all pleural procedure sites and a minimum field size of 4 cm\textsuperscript{2} for simple aspiration/biopsy and 6 cm\textsuperscript{2} minimum for chest drain/thoracoscopy is needed to maximise patient benefit from radiotherapy. Larger field sizes are used if there are adjacent biopsy or aspiration sites, which all need encompassing within the treatment field. It is now our practice to mark all biopsy and aspiration sites in potential mesothelioma cases with Indian ink, so that radiotherapy fields can be adjusted to reliably incorporate all these sites. Any further chest interventions outside the radiotherapy field should be followed with further radiotherapy.

The indwelling pleural catheters used for persistent pleural fluid and trapped lung are tunnelled semi-permanent catheters which patients themselves can access and drain fluid from as required.\textsuperscript{7} There is a permanent tract created by these catheters. The likelihood of mesothelioma seeding down these tracts whilst the catheter is in situ is unknown. The use of radiotherapy for prophylaxis against tract tumours whilst the catheter is in situ is also untested, as are the effects of radiotherapy on indwelling catheters. The patient in our cohort who developed tumour around the catheter insertion point had persistent pleural fluid leakage problems around the drain exit point since it was inserted. It was postulated that the fluid leak may have contributed to the tumour growth, by allowing seeding of mesothelioma cells along the track. He responded well to radiotherapy, with no adverse effect on the catheter, despite high radiotherapy doses. The nodules which developed over the tumour 7 months after the radiotherapy were most likely due to the progression of his underlying disease. Similar tumour growth due to seeding from a fluid leak along a catheter track has been previously described in mesothelioma, in a case where the chest drain was used for intrapleural chemotherapy.\textsuperscript{8} It is not our routine practice to irradiate indwelling pleural catheters.

In conclusion, radiotherapy is well-tolerated and effective at preventing mesothelioma seeding at chest instrumentation sites in subjects who do not have clinical evidence of track tumour growth already present at the time of treatment.

References