Prevention of Malignant Seeding After Invasive Diagnostic Procedures in Patients With Pleural Mesothelioma* 
A Randomized Trial of Local Radiotherapy

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The purpose of this randomized prospective study was to assess the efficacy of local radiotherapy in preventing malignant seeding along invasive diagnostic procedures (cytology, needle biopsy, thoracoscopy, or chest tube placement) in patients with malignant pleural mesothelioma. Forty consecutive patients with histologically proven malignant mesothelioma were enrolled. Twenty patients received three daily sessions of radiotherapy at a dosage of 7 Gy 10 to 15 days after thoracoscopy. The other 20 patients did not receive radiotherapy. None of the 20 patients treated developed entry tract metastasis. In contrast, 8 of the 20 (40%) patients who were not treated developed metastases. These findings confirm the efficacy and safety of early local radiotherapy in preventing malignant seeding after invasive diagnostic procedures in patients with malignant pleural mesothelioma. (CHEST 1995; 108:754-58)

Key words: local radiotherapy; pleural mesothelioma; subcutaneous metastases; thoracoscopy

Malignant seeding along the tracts of cytology or biopsy needles, chest tubes, thoracoscopy trocars and surgical incisions is a common complication of diagnostic and therapeutic procedures in patients with malignant pleural mesothelioma.1-3 Metastases present as exceedingly painful subcutaneous nodules varying from 1 to 4 cm in diameter. On the back, these lesions are particularly uncomfortable and often prevent patients from sleeping (Fig 1).4,5 Surgical resection is seldom feasible and radiotherapy is ineffective.

In the literature, the mean incidence of malignant seeding is 19% with extremes of 2 and 51%.1,6-12 In contrast, seeding is rare in patients with secondary pleural cancers.13-15 Despite this risk, percutaneous procedures, especially thoracoscopy, are needed to identify patients with early-stage cancer who can benefit from recent therapeutic advances.16-18 Indeed, promising results have been obtained with intrapleural cytokine treatment in stage IA mesotheliomas.19-21

The purpose of this randomized study was to assess the efficacy of local radiotherapy in preventing malignant seeding along trocar and drainage tube tracts in patients with malignant mesothelioma.

Methods

Patients

This study included 40 consecutive patients (33 men and 7 women; mean age, 66±3 years) with pleural mesothelioma whose life expectancy was over 3 months at the time of diagnosis. All patients had undergone pleural cytologic study and Abrams needle biopsy within 1 month before thoracoscopy; and puncture sites were still clearly visible. Thirteen patients had positive cytologic findings (meaning detection of "malignant cells") and 6 had positive needle biopsy results.

Thoracoscopy was performed for diagnosis, staging, or talc pleurodesis. Diagnosis of malignant mesothelioma was confirmed by the French National Panel of Pathologists. Disease staging was based on thorascopic findings, ie, degree of extension and macroscopic appearance of lesions;22 CT scan of the chest, hepatic ultrasonography, bone scintigraphy, and CT scan of the brain. The classification system has been described elsewhere.20

In 33 of 40 patients talc pleurodesis was performed at the end of thoracoscopy to prevent recurrent effusion. Twenty-two patients subsequently underwent three to four courses of single-agent chemotherapy and 6 patients underwent multiagent chemotherapy (vinodesine, cisplatin, and epirubicin). Neither regimen was successful. Seven patients received no further treatment.

All patients were regularly examined to detect subcutaneous nodules at procedure scar sites.

Local Radiotherapy

Radiotherapy was performed after healing of the wounds, ie, 10 to 15 days after thoracoscopy. The radiotherapy technique was designed to deliver a dosage of 21 Gy over 3 days (3×7 Gy) to the thoracic wall, which is equivalent to 45 Gy in 4.5 weeks. Beta-rays were delivered by an electron source of 12.5 to 15 mev depending

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Figure 1. Large parietal tumor invasion developed on a needle tract after simple thoracentesis.

on the depth of the irradiation (mean, 3 cm) required in function of the thickness of the skin and pleura. A slice of paraffin 1 cm thick brought to the skin the reference isodose of 90% (Fig 2). All procedure scar sites (cytology, needle biopsy, drainage, and trocars) were included in square exposure zones ranging from 16 to 100 cm² (Fig 3).

Results

Patients were randomly divided into two groups of 20. In one group, radiotherapy was performed and in the other it was not. As shown in Table 1, there was no significant difference between these two groups with regard to clinical status, treatment, or median survival.

None of the patients in the treatment group developed subcutaneous nodules. Conversely, eight patients (40%) in the untreated group developed subcutaneous nodules (p<0.001) at entry sites of thoracoscopy trocars or chest tubes (five patients) and/or cytology or biopsy needles (seven patients).

Table 2 shows the characteristics of the patients who developed subcutaneous nodules. The mean interval between the procedure and appearance of nodules was 6 months (range, 1 to 13 months). There was no correlation between occurrence of nodules and positive cytologic study or Abrams needle biopsy, histologic type, disease stage, or subsequent treatment. Similarly, occurrence of nodules was not related to the size of the tracts, since there was no significant difference between the number of metastases associated with chest tube sites and other entry sites.

In all cases, tolerance of local radiotherapy was excellent. Skin discoloration was noted in all patients, but edema or inflammation was not observed.

Discussion

This study confirms the efficacy and safety of local radiotherapy in preventing tract metastases after cytologic study, needle biopsy, thoracoscopy, or chest tube placement in patients with malignant mesothelioma.
This result contrasts sharply with the poor effectiveness of radiotherapy for pleural mesothelioma. Response rates have never exceeded 15%. In their series including 49 patients treated by radiation therapy, surgical resection, and chemotherapy, Mattson et al noted one complete and five partial pleural responses, but survival was not prolonged. Other studies have confirmed that radiotherapy alone or in association with surgery or chemotherapy has no effect on survival in patients with mesothelioma. The only beneficial effects that have been reported inconsistently are relief of chest pain and dyspnea.

Additionally, because of the need for high doses (40 to 80 Gy) and/or extensive target areas, radiotherapy has resulted in serious complications in patients treated for pleural mesothelioma. Radiation-induced pulmonary fibrosis is almost always observed and in some cases has resulted in complete destruction of the irradiated lung. Fatal hepatitis (one case) and myelitis (one case) have also been reported. In our experience, high-dose radiotherapy of the hemithorax did not prevent neoplastic seeding along needle tracts, presumably because penetration was too deep. Similarly, radiotherapy was not effective for the treatment of subcutaneous nodules.

Because it involves a limited area in terms of breadth (100 cm²) and depth (3 cm), the preventive local radiotherapy technique described in the present study is safe. Effectiveness depends on two conditions. First treatment must be performed early, ie, within 10 to 15 days after thoracoscopy and less than 1 month after needle biopsy. The second condition of success is irradiation of all procedure scars. In this regard, it is important to mark all puncture sites with India ink.

Two nonexclusive mechanisms could account for the
effectiveness of local radiotherapy. Local radiation may kill migrating cells before they are able to form a resistant colony. Because sensitivity to radiotherapy depends on the tumor size, it is reasonable to assume that isolated cells would be more vulnerable than clusters measuring 2 to 300 μm. The second explanation is that irradiated tissue may be an unfavorable environment for malignant seeding. Experimental evidence for a “tumor bed effect” of irradiation has been reported.\(^{30-33}\)

Growth of various tumor-cell lines is significantly delayed after implantation in preirradiated sites as compared with normal tissue. This effect starts at a dose of 10 Gy,\(^{31}\) and peaks between 20 and 30 Gy.\(^{32}\) No further inhibition of tumor growth is obtained at doses above 30 Gy.\(^{30}\) The mechanisms usually proposed to explain tumor bed effect are an alteration of the blood supply in the irradiated zone that results in a decrease in angiogenesis and thus in the supply of oxygen\(^ {34,35}\) and growth factors.\(^ {30}\) Radiation-induced fibrosis could also be a limiting factor for tumor growth.\(^ {30}\)

The findings of this study indicate that local radiotherapy should be performed routinely when diagnosis of mesothelioma has been confirmed or suspected despite preliminary results in favor of an adenocarcinoma. The optimal delay after thoracoscopy is 10 to 15 days in order to irradiate seeded tumor cells as soon as practicable after healing of the thoracoscopy scar. The number of invasive diagnostic procedures performed in patients with mesothelioma should be limited and entry sites should be grouped so that they can be irradiated within one or two fields.

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