Pulmonary Reaction to Upper Mantle Radiation Therapy for Hodgkin's Disease*

Guillermo A. do Pico, M.D.; Albert L. Wiley, Jr., M.D.; Pradeep Rao, M.S.; and Helen A. Dickie, M.D.

To study the effects of upper mantle radiation therapy on pulmonary function, forced expiratory volume in one second (FEV1), vital capacity (VC), inspiratory capacity (IC), diffusing capacity for CO (DLCO) and diffusion per unit of alveolar volume (DLco/VA) were determined in 28 patients with Hodgkin's disease, stages 1-3, before therapy and at regular intervals thereafter. Within the first year of follow-up there were significant declines in DLco, VC, and IC, whereas there were no significant changes in FEV1 or DLco/VA. DLco showed the greatest decline in the largest number of subjects (22/28). Eleven of the 22 had 20 to 60 percent decline of DLco from baseline. The maximum mean decline in DLco was -12.7 ± 3 percent at the 87th ± 3 days from initiation of therapy.

Supervoltage mantle field irradiation is recognized as an effective and well-tolerated method of therapy for supradiaphragmatic Hodgkin's disease.1 Technical improvements introduced over the past decade result in a reduction in the incidence of symptomatic radiation pneumonitis and pericarditis;1 however, a few patients still experience significant and even fatal radiation pneumonitis.1,2 Pulmonary function disturbances induced by radiation may exist without clinical or radiologically demonstrable abnormalities. Lung function abnormalities secondary to radiation for lung or breast carcinoma are well documented.3,4 This report presents the results of our prospective study of the effects of upper mantle radiation therapy for Hodgkin's disease, stage 1-3, on lung function where limited information is available. The study was prompted by the death of a patient from radiation pneumonitis, following therapy for stage 1 Hodgkin's disease. The mediastinum of this patient was treated "prophylactically," and a relatively small amount of lung was also irradiated. The diffuse morphologic changes found on autopsy suggested to us that radiation injury in mantle therapy might extend beyond the field of direct irradiation.

**MATERIAL AND METHODS**

Twenty-eight patients with Hodgkin's disease, stages 1, 2 and 3, (Ann Arbor classification)5 who received upper mantle therapy from a cobalt source, were studied between October, 1970 and August, 1974 for at least six months. This study excluded patients younger than 15 years, those who had been observed for less than six months, those who could not be tested at regular intervals, and those who had received whole lung radiation because of tumor spread into the lung. Among the 28 patients studied, there were 16 men and 12 women between 15 and 62 years of age. Staging was established by physical examination, chest radiogram, lymphangiography and exploratory laparotomy. Five patients were stage I, 12 stage II, and 11 stage III. Eighteen of the 28 patients had intrathoracic disease by chest radiograph.

All of the patients were treated according to "standard mantle" therapy techniques6 on a 10,000 Ci Picker cobalt unit. Accordingly, lead blocks (half value layer thickness or 3 percent transmission) were tailored to spare as much lung parenchyma as possible. The source size was 2 × 2 × 2 cm. Source to treatment distance was 160 cm. Lead block-to-skin distance averaged from 30 to 40 cm, depending upon the size of the patient. The total dose of radiation ranged between 3,500 and 4,785 rads and a daily dose rate of 180 to 200 rads.

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Reprint requests: Dr. do Pico, 504 North Walnut, Madison, Wisconsin 53706.

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per day. In a few instances, a split of several weeks in the course of radiation was allowed for tumor regression. Weekly checks on port films were made to assure reproducibility. Subsequently, 22 patients also received additional periarterial abdominal irradiation which, in seven patients, included the splenic pedicle.

Twenty-five patients were followed-up for 12 to 16 months or longer and three for six to eight months.

Pulmonary function studies included the measurements of inspiratory capacity (IC), vital capacity (VC), forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), FEV₁/FVC percent measured on a 13.5 liter Collins water spirometer, *diffusing capacity (D_{L}/V_A)* for carbon monoxide, and the alveolar volume by the conventional single breath CO-He method* and the diffusion/alveolar volume ratio. In a few instances, when anemia had developed, D_{L} values were corrected for hemoglobin concentration using the equation of Dinakara and collaborators.*

Pulmonary function was tested before and within two weeks of cessation of radiation therapy, then at approximately two-month intervals during the first year, and less frequently thereafter. Baseline values were those obtained within the week prior to or within the first three days of therapy.

Concurrent with the pulmonary function studies, the patient's clinical status was evaluated by history, examination, chest radiographs, hemoglobin and leukocyte count. Four patients received chemotherapy with cyclophosphamide, vincristine, procarbazine and prednisone (COPP) more than a year after radiation therapy. One patient received COPP four months after therapy.

RESULTS

The mean and 1 SD baseline pulmonary function test ranges were: FEV₁/FVC percent *X 78 ± 10; IC *X 93 ± 18.7 percent of predicted; VC *X 109 ± 22.4 percent of predicted and D_{L} *X 102 ± 24 percent of predicted. Abnormal FEV₁/FVC percent of less than 70 was found in seven patients, but only two patients had values below 65 percent. Values of less than 80 percent of predicted IC, VC and D_{L} were found in four, two and three patients respectively.

After upper mantle radiation, there was a significant mean decline in diffusing capacity (*P < 0.001*), inspiratory capacity and vital capacity (*P < 0.01*), but no significant changes in FEV₁ or D_{L}/V_A. Figure 1 shows the mean and one standard error in the percentage of change in function grouped within 60-day periods. The location of the data in the horizontal axis corresponds to the average time of the testing within the 60-day period which corresponds approximately to two-month intervals during the first year. The data averaged at 60-day intervals after the 360th day varied greatly; therefore, no conclusions were made from group data beyond this point, but data points are presented to illustrate the course of the function changes. Of the pulmonary functions tested, D_{L} showed the greatest decline in the largest number of patients. The maximum mean


Figure 1. Mean and 1SD of the percentage of change in lung function grouped within 60-day periods. The location of the data in the horizontal axis corresponds to the average time of testing within the 60-day period which correspond approximately with the cessation of therapy and two-month intervals thereafter during the first year. D_{L} = diffusing capacity; D_{L}/VA = D_{L} to alveolar volume ratio; VC = vital capacity; IC = inspiratory capacity; FEV₁ = forced expiratory volume in one second.

decline in D_{L} was seen between the 80th and 150th day (three to five months) after the initiation of therapy, returning to within 5 percent of pretreatment level by the end of the year. The maximum mean decline was -12.7 percent, ±3 percent found at the 87th day ± three days. Eight of the 28 pa-
patients showed a greater than 10 percent decline in $D_L$ at the end of the radiation therapy.

Individual changes in $D_L$ varied greatly, but several trends could be recognized (Fig 2). There were six patients whose $D_L$ did not change significantly or actually increased. More commonly, (22/28) the $D_L$ declined more than 10 percent, as in patients 7, 9, and 10, and it either returned to pretreatment level (cases 7 and 9) or remained low (case 10). The maximum individual change in $D_L$ during the first 12 months after radiation in some individuals exceeded 50 percent (Fig 3). In 22 patients, the fall in $D_L$ was greater than 10 percent (Table 1). In half, (11/22) the maximum decline was greater than 20 percent. In almost half of the patients (12/22) the $D_L$ returned to pretreatment levels within the first year, whereas in the others, (10/22) although 10 to 20 percent improvement was frequently found, $D_L$ failed to return to pretreatment level. The functional impairment was not more severe or prolonged in those patients with more extensive stage 3 disease.

To analyze the factors or events that may correlate or influence the development of lung function abnormalities, we used a Chi-square analysis, grouping patients according to whether or not they: 1) had radiologic evidence of intrathoracic disease (mediastinal or paratracheal), 2) had had post-radiation respiratory symptoms and 3) had post-radiation chest radiograms compatible with radiation injury characterized by stringy linear densities by the hila extending into the upper lobes (Table 2). The development of functional loss seemed to be independent of the presence or absence of intrathoracic disease. There was no significant correlation between the loss of function and either post-radiation respiratory symptoms or post-radiation chest radiogram changes compatible with radiation pneumonitis. Note, however, that all those showing radiographic evidence of radiation injury had reduction in $D_L$.

**DISCUSSION**

The results of our studies showed that impairment of diffusing capacity and loss of lung volume (IC and VC) developed in most patients who received extended upper mantle radiation therapy for Hodgkin's disease despite conventional lung shielding. The effects on lung function were prolonged and occasionally severe, but in general, they were transient and clinically mild. In certain cases, however, the functional impairment persisted or progressed for several years. The functional impairment was not more severe or prolonged in those patients with more extensive stage 3 disease.

![Figure 2. Course of individual changes in diffusing capacity in cases 7, 9, and 10.](image1)

![Figure 3. The maximum individual change in $D_L$ within the first year post-radiation.](image2)
Decline in vital capacity affects the available surface for gas exchange and is frequently seen as a consequence of the radiation reaction. In this study, the reduction in alveolar volume appears to be responsible for the decline in diffusion since the ratio of diffusion per unit of alveolar volume \(D_L/V_A\) did not change significantly. It is likely that the thickening of alveolar septa by edema, mononuclear cellular infiltrates and fibroblasts, as well as the filling of alveolar spaces with desquamated cells, fibrin-rich deposits and hyaline membranes characteristic of radiation pneumonitis, decrease \(D_L\) not only by reducing the surface for gas exchange (reduced alveolar volume) but also by increasing the diffusion pathway. Loss of the capillary surface for gas exchange can also cause a reduction in \(D_L\), and there is evidence indicating that pulmonary perfusion is impaired one to two months after irradiation. 

Carmel and Kaplan noted that there is still a significant incidence of symptomatic pulmonary radiation reaction despite lung shielding because large portions of the lung must still lie within the field of irradiation. There is no doubt that radiation injury occurs on the lung directly irradiated, but there is reason to suspect that despite adequate lung shielding, a diffuse lung reaction beyond the field of irradiation can occur and may be due to scatter radiation. Bennett and colleagues found that while small doses of scattered radiation reaching the contralateral (not directly irradiated) lung, were usually innocuous, severe, diffuse pneumonitis occurred in some individuals. The magnitude of the \(D_L\) changes found in some of our patients suggests that the pulmonary reaction was likely to be diffuse and that it extended beyond the lung directly irradiated. Morphologic evidence of these diffuse changes was present in the patient who prompted our prospective studies (see appendix).

Recently, Gray and Prosnitz reported that up to 20 percent of the total dose delivered by x-ray linear accelerator was scattered into the mid-lung. Thus, in our patients, although the lungs were shielded according to standard methods, the primary transmission may have been 200 rads and the scattered dose to the lungs an additional 800 rads so that the total dose to the "shielded" lung could have been approximately 1,000 rads. It has been reported that doses as small as 600 rads can cause pneumonitis and can occasionally result in severe fatal radiation pneumonitis. Chemotherapeutic agents and previous radiation are among the factors considered to increase the lung susceptibility to radiation injury. None of these factors was present in our patient with fatal diffuse radiation pneumonitis, but in this case, as in others, it is tempting to believe that scattered radiation may account for some of the reported widespread reactions to radiation.

Current accessibility to computerized axiotomographic scans and three-dimensional treatment planning systems (not available at the time of our study), now facilitate the calculation of the maximum and minimum dose to lung directly or indirectly irradiated and of integral doses to these regions. This should allow more meaningful correlations between pulmonary function changes and radiation doses. A reasonable study in the future would be to evaluate pulmonary function before and after radiotherapy and to correlate these changes with the volume (as determined by computerized axiotomography) of lung directly and indirectly irradiated.

An important conclusion from our study is that it confirms that some patients have clinically or roentgenologically unrecognized damage to the lungs from mantle therapy, and that the appropriate pulmonary function tests can detect these patients. Physicians should be aware that the functional changes may be present for many months after radiation therapy, and that in these patients, superimposed

### Table 1—Changes in Diffusing Capacity during First Year of Follow-Up

<table>
<thead>
<tr>
<th>Hodgkin’s disease stage</th>
<th>No.</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Decline 10-19.9 percent</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Decline &gt;20 percent</td>
<td>11</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>5</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Evans found that changes in vital capacity were transient, and as in our study, the maximum decline in function was reached in four to six months and returned to pretreatment levels by the eighth month.

The measurement of diffusing capacity for CO, appears to be the most sensitive of the commonly available noninvasive methods for following the effects of radiation injury. In this study, the reduction in alveolar volume appears to be responsible for the decline in diffusion since the ratio of diffusion per unit of alveolar volume \(D_L/V_A\) did not change significantly. It is likely that the thickening of alveolar septa by edema, mononuclear cellular infiltrates and fibroblasts, as well as the filling of alveolar spaces with desquamated cells, fibrin-rich deposits and hyaline membranes characteristic of radiation pneumonitis, decrease \(D_L\) not only by reducing the surface for gas exchange (reduced alveolar volume) but also by increasing the diffusion pathway. Loss of the capillary surface for gas exchange can also cause a reduction in \(D_L\), and there is evidence indicating that pulmonary perfusion is impaired one to two months after irradiation.

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### Table 2—Relation of Changes in \(D_L\) with Other Clinical Findings Within the First Year of Follow-Up

<table>
<thead>
<tr>
<th>Findings</th>
<th>Present</th>
<th>No Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. with</td>
<td>All (\Delta D_L &gt;10%)</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>7</td>
<td>6 (83)</td>
</tr>
<tr>
<td>Intrathoracic disease</td>
<td>18</td>
<td>15 (86)</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td></td>
<td></td>
</tr>
<tr>
<td>compatible with</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>radiation injury</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

( ) Percentage with \(D_L\) decline greater than 10 percent with or without clinical manifestation.

*No significant difference using Chi square analysis.

†No significant difference using Fisher exact test.

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respiratory or cardiac complications, additional lung irradiation, therapy with chemotherapeutic agents known to induce pulmonary reaction, or corticosteroid withdrawal from a program may be poorly tolerated.

APPENDIX

A 31-year-old man with Hodgkin’s disease diagnosed by biopsy of a painless left cervical node was treated with extended upper mantle radiation, as described by Edland,6 using a styrofoam block and mid-mediastinal dose of 4,000 rads. About two months after the initiation of treatment, he noticed progressive dyspnea. There was no history of fever or chills. By the third month, he was admitted to the University Hospitals in respiratory failure. His arterial oxygen tension, (PaO2) was 26 mm Hg and the PCO2 was 21 mm Hg. There were bilateral diffuse pulmonary infiltrates before oxygen was administered. Despite intensive respiratory support therapy, he died ten days later. On autopsy, there was diffuse pneumonitis characterized by extensive consolidation with swelling and thickening of alveolar septa with fibroblastic proliferation, intra-alveolar fibrinous deposits and hyaline membrane formation, abundant desquamation of pneumocytes and macrophages. These changes, compatible with radiation pneumonitis, were diffuse and affected the lower lobes as well as other areas of the lungs that had not been directly radiated and had been protected from radiation by conventional shielding. No errors in dosimetry were found after extensive post-mortem calculations.

REFERENCES