Effects of Proton and Combined Proton/Photon Beam Radiation on Pulmonary Function in Patients With Resectable but Medically Inoperable Non-small Cell Lung Cancer*

Reiner B. Bonnet, MD; David Bush, MD; Gregory A. Cheek, MD, FCCP; Jerry D. Slater, MD; David Panossian, MD, FCCP; Christian Franke, MD; and James M. Slater, MD

Study objectives: We evaluated the effects on pulmonary function of irradiating lung cancer with protons alone or protons combined with photons.

Design: Prospective phase I/II study.

Setting: University medical center.

Patients and interventions: Ten patients with stage I-II non-small cell lung cancer (NSCLC) and FEV1 ≤ 1.0 L were irradiated with protons to areas of gross disease only, using 51 cobalt gray equivalents (CGE) in 10 fractions (protocol 1). Fifteen patients with stage I-IIIA NSCLC and FEV1 > 1.0 L received 45-Gy photon irradiation to the primary lung tumor and the mediastinum, plus a 28.8-CGE proton boost to the gross tumor volume (protocol 2).

Measurements: Pulmonary function was evaluated prior to treatment and 1 month, 3 months, and 6 to 12 months following irradiation.

Results: In patients receiving protocol 1, no significant changes in pulmonary function occurred. In patients receiving protocol 2, at 6 to 12 months, the diffusion capacity of the lung for carbon monoxide had declined from 61% of predicted to 45% of predicted (p < 0.05), total lung capacity had declined from 114% of predicted to 95% of predicted (p < 0.05), and residual volume had declined from 160% of predicted to 132% of predicted (p < 0.05). Airway resistance increased from 3.8 to 5.2 cm H2O/L/s (p < 0.05). No statistically significant changes occurred in vital capacity, FEV1, or PaO2.

Conclusions: Our observations indicate that it is feasible to apply higher-than-conventional doses of radiation at a higher-than-conventional dose per fraction without excess pulmonary toxicity when conformal radiation techniques with protons are used.

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Key words: irradiation; lung cancer treatment; non-small cell lung cancer; photon; proton; radiation

Abbreviations: ABG = arterial blood gas; CGE = cobalt gray equivalent; CHF = congestive heart failure; DLCO = diffusion capacity of the lung for carbon monoxide; IC = inspiratory capacity; Kco = Krogh factor; LLUMC = Loma Linda University Medical Center; MBC = maximum breathing capacity; NSCLC = non-small cell lung cancer; PFT = pulmonary function testing; Raw = airway resistance; RV = residual volume; TLC = total lung capacity

Lung cancer is the leading cause of cancer death in the United States and remains a challenge to all clinicians who treat it. In 1996, the estimated occurrences of morbidity and mortality from lung cancer were 177,000 cases and 158,700 deaths, respectively.1 Approximately 80% of patients had non-small cell lung carcinoma (NSCLC); approximately 20% had the small cell type.2,3

The standard treatment for patients with stage I, stage II, and selected stage IIIA NSCLC is surgical resection.1–8 However, many patients with potentially resectable NSCLC are found to have inoperable conditions because of insufficient pulmonary reserve or other medical conditions.9 One of the proposed therapies for this group of patients might be radiation. Within the therapeutic range of doses usually administered for radiation therapy for unresectable lung cancer, virtually 100% of the lung parenchyma

*From the Department of Pulmonary Medicine (Dr. Bonnet), Zentralklinik Bad Berka GmbH, Bad Berka, Germany; and Division of Pulmonary and Critical Care Medicine (Drs. Cheek, Panossian, and Franke), and Department of Radiation Medicine (Drs. Bush, J.D. Slater, and J.M. Slater), Loma Linda University, Loma Linda, CA.

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Correspondence to: Reiner B. Bonnet, MD, Zentralklinik Bad Berka GmbH, Klinik für Pneumologie, Robert Koch Allee 9, 99438 Bad Berka, Germany; e-mail: r.bonnet.pn@zentralklinik-bad-berka.de
in the treatment field reacts to radiation. Pathologic changes often supervene and are frequently clinically defined as early (acute radiation pneumonitis) or late (fibrosis). During the acute phase, in many cases, demonstrable abnormalities on conventional radiographs and physical findings on routine chest examinations are absent. High-resolution CT of the chest and pulmonary function testing (PFT) are more sensitive procedures for determining the presence and extent of damage.

Radiation Therapy With Protons

One of the disadvantages of radiation therapy for NSCLC compared to surgical resection is reduced long-term survival, resulting from local failure. Radiation Therapy Oncology Group studies have indicated that higher doses of radiation, up to 60 Gy, are associated with increased survival. When doses have been increased to between 65 Gy and 70 Gy with conventional radiation, further survival benefits have not been demonstrated, presumably because significant morbidity supervenes after damage to surrounding tissues and offsets any possible benefit of increased local tumor control. This limitation is especially true in patients with severe COPD, since there is no pulmonary reserve to compensate for any degree of radiation pneumonitis or fibrosis. Thus, a treatment designed to deliver higher doses of radiation to sites involved with tumor, while not delivering an excessive dose to surrounding normal tissues, may increase locoregional control and survival in patients not able to have surgical resection.

Particle beam therapy with protons is one way of accomplishing this goal. In conventional photon irradiation, the highest radiation dose is delivered directly on entry into the body. While the photon beam traverses the body, the tissue dose continually declines until the beam exits the body opposite to its entry site. In contrast, protons traveling in tissues follow a predetermined track, have minimal side scatter, and deliver most of their energy near the end of their track (Fig 1). This property is obtained at any prescribed depth and thus may be used to shape the dose distribution three dimensionally to fit virtually any tumor volume with very high precision.

Since to our knowledge proton beam radiation has never been clinically evaluated in the treatment of lung cancer, a prospective phase I/II study was initiated at Loma Linda University Medical Center (LLUMC), after approval by the institutional review board, to evaluate the pulmonary toxicity of the modality and to collect initial data on tumor response and survival. Reports on radiographic manifestations of pulmonary damage and on survival have been previously published. This article reports the results of phase I of the study: the effects observed from irradiation of lung cancer with protons alone (tumor alone) in patients with very poor pulmonary function, or protons combined with photons (tumor and mediastinum) in patients with acceptable pulmonary function, as reflected in pulmonary symptoms and function during the first 12 months following treatment.

Materials and Methods

Patient Eligibility Requirements

Between August 1994 and January 1998, 37 patients with resectable but medically inoperable NSCLC were treated at LLUMC, either with proton radiation therapy alone when very poor pulmonary function was present (protocol 1), or with combined photon beam and proton beam therapy (protocol 2). To be included into the pulmonary function substudy, the patients must have agreed to have their PFT performed at the indicated intervals at Loma Linda University. This was believed
to be necessary to ensure comparability of the pulmonary function data. Twenty-five patients fulfilled this criterion and were entered. There were 17 female and 8 male patients (mean age [range], 71.3 years [52 to 85 years]). All 25 patients had a history of heavy smoking, with a mean (range) of 75 pack-years (20 to 200 pack-years).

Patients were eligible for protocol 1 if they had tumor in stages T1N0M0 and had FEV1 values ≤ 1.0 L, or any medical contra-indications for lung resection. Patients with N1 status were considered eligible if the lymph node and the primary tumor could be included in one radiation field. Ten persons met these criteria. Patients were eligible for protocol 2 if they had tumor in stage T1–3N0–2M0 and FEV1 > 1.0 L prior to irradiation; 15 persons qualified for protocol 2 and were entered into the study.

Tissue diagnoses of NSCLC had to be established in all instances prior to radiation, and informed consent had to be signed. Further criteria for both protocols are as follows: age ≥ 18 years, Karnofsky index > 60, medical contraindication or patient refusal to surgery, no prior radiation therapy to the chest, no chemotherapy within the past 6 months, no weight loss > 10% of body weight, and no other malignancies within the past 5 years.

Pretreatment Evaluation

Initial evaluation consisted of history and physical examination, weight, assignment of a Karnofsky performance score, and a modified dyspnea scale score (Table 1),24 high-resolution CT of the chest (including the liver and adrenals using regular resolution), conventional chest radiographs, CBC count, and random chemistry profile. PFT consisted of arterial blood gas (ABG) analysis (model 555; Chiron Diagnostics; Norwood, MA), spirometry, body plethysmography including total airway resistance (Raw) [Jaeger Bodytest; Jaeger; Würzburg, Germany], and single-breath diffusion capacity of the lung for carbon monoxide (DLCO) [PK Morgan; Chatham, England]; all were performed according to American Thoracic Society standards.23,20

Technique of Proton Irradiation

The proton treatment center at LLUMC is the first such facility that is integrated into a hospital setting.25 Proton treatments can be delivered to any part of the body due to a gantry system with 360° rotation capability; the system has multiple treatment beam energies.

Protons are generated in an ionization chamber but possess only a low energy level of 35 keV. To energize them sufficiently to be medically useful, they are injected into a synchronotron and accelerated up to 250 MeV. They are extracted as 300-ns pulses, guided to the treatment room by magnetic fields, and aimed at the tumor using the gantry.

During radiation, the patient is fixated in an individually manufactured body cast. Based on pretreatment planning, an individualized wax bolus and lead apertures are placed into the radiation beam proximal to the patient, to modulate the depth of the Bragg peak and the edges of the radiation field, respectively. The necessary energy level of the protons is chosen based on the position of the tumor in the body. Using these modalities, the proton beam is three-dimensionally configured to match tumor shape and tissue heterogeneities. Around the tumor, an additional margin is included in the radiation field to account for tumor motion due to respiration. The exact dimensions of this margin are determined fluoroscopically. Dose-volume histograms are obtained for all cases.

Treatment Procedures

Protocol 1: Proton therapy was delivered to sites of gross disease; treatment volumes included appropriate margins for respiratory motion. The total dose was 51 cobalt gray equivalent (CGE)22 in 10 fractions over 2 weeks. The treatment volume excluded the trachea, esophagus, and heart.

Protocol 2: These patients received photon irradiation that covered the primary lung tumor and the mediastinum, plus a proton beam boost to the gross tumor volume. The latter was administered concurrently with photon irradiation in the last 3 weeks of treatment, with at least a 6-h interval between the two daily fractions. Photons were administered at 1.8 Gy, and protons were administered at 1.8 CGE per fraction. The total dose to the mediastinum and tumor volume with photons was 45 Gy; the total dose to the gross tumor volume with protons was 28.5 CGE; combined, 73.8 Gy of photon and proton irradiation was administered over a course of 5 weeks.

Follow-up Study

Patients were seen 4 weeks and 3 months following completion of treatment, and then at 3-month intervals up to 12 months, according to the pretreatment testing profile. Follow-up is ongoing with regards to survival data.

Statistical Procedures

Within each protocol population, changes in the absolute values of the following variables were compared by means of the repeated-measures analysis of variance and post hoc tests according to Newman-Keuls: FVC, total lung capacity (TLC), inspiratory capacity (IC), residual volume (RV), Raw, FEV1, DLCO, Krogh factor (KCO), and PaO2. No statistical analyses were performed between the patients in protocol 1 and protocol 2 since this was not the objective of the study (different selection criteria applied).

RESULTS

One patient withdrew consent to the study after receiving radiation therapy. Of the remaining 24 patients, 10 patients were treated according to protocol 1 and 14 patients were treated according to protocol 2. In protocol 1, nine patients had stage I tumors and one patient had a stage II tumor. In protocol 2, eight patients had stage I tumors, two patients had stage II tumors, and four patients had stage IIIA tumors.

Data at month 1 are available from 21 patients, since 3 patients did not report for testing. At month

<table>
<thead>
<tr>
<th>Table 1—Modified Dyspnea Scale Score to Evaluate Patient’s Subjective Experience of Dyspnea*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Point Value</strong></td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
</tr>
</tbody>
</table>

*Based on Mahler and Wells.24
3. 22 patients could be evaluated. One patient had died of congestive heart failure (CHF), and one patient withdrew consent for further participation. The evaluation for late toxicities (months 6 to 12) could be obtained on 18 patients. Three further patients had died, and one further patient had withdrawn consent.

Nine of 10 patients (90%) treated according to protocol 1 had severe COPD and 1 patient had severe CHF. Of the protocol 2 patients, two patients (14.3%) had COPD, one patient (7.1%) had asthma, one patient (7.1%) had obstructive sleep apnea and was undergoing treatment for that condition, and two patients (14.3%) had CHF. The mean (range) Karnofsky performance scores of the patients in protocol 1 and protocol 2 were 86 (70 to 100) and 88 (70 to 100), respectively, at baseline; and 84 (70 to 100) and 76 (50 to 100), respectively, at 6 to 12 months following radiation therapy.

Clinically acute radiation pneumonitis developed in two patients. Both patients had received photon therapy with proton boosting (protocol 2). In one case, the pneumonitis clinically resolved with steroid therapy; in the other case, pulmonary fibrosis developed. In a third patient who had also received combined proton/photon treatment, pulmonary fibrosis developed at 6 months without prior clinical signs of acute radiation pneumonitis. There were no treatment-related deaths.

The mean dyspnea scores in patients receiving protocol 1 did not change significantly: they were 3.0 at baseline, month 1, and month 3, and 2.8 at months 6 to 12. In patients receiving protocol 2, they were 2.1, 2.1, 2.7, and 3.3, respectively (p < 0.5), documenting increased dyspnea perception in the late phase following combined proton/photon beam radiation.

Changes in pulmonary function are summarized in Tables 2, 3. None of the patients had an acute exacerbation of their underlying disease at the time of PFT. In patients receiving protocol 1, no statistically significant decline occurred in FVC, TLC, RV, FEV1, DLco, and PaO2 at 1 month, 3 months, or 6 to 12 months after completion of radiation treatment. Raw remained statistically unchanged. IC showed a small but statistically significant decline, which was most probably due to an increase in the functional residual capacity rather than to pulmonary fibrosis since TLC had not declined. One patient, who was receiving continuous oxygen therapy prior to and following radiation and, therefore, had ABG evaluations only with supplemental oxygen, was excluded from the statistical analysis of the PaO2 values. In two patients receiving protocol 1, baseline DLco (Kco) could technically not be measured due to an extremely low FVC. Due to the high variability and the technical limits in measuring the DLco (Kco) in this very sick patient population (FEV1 range, 0.28 to 1.34 L), the results of these values should not be overinterpreted.

In patients receiving protocol 2, there were no significant changes in lung volumes during the early and intermediate phase except for the IC. During the late phase, however, TLC, IC, and RV significantly decreased by 16.8%, 20%, and 17.7%, respectively. FVC showed no statistically significant change. FEV1 as a parameter for airway obstruction remained unchanged while Raw increased. The DLco as a sensitive parameter of diffusion defects showed in the early and intermediate phases a trend and in the late phase a statistically significant reduction from 61% to 45% of predicted. Kco showed a statistically significant decline in the early, intermediate, and late phases. PaO2 values did not change.

Table 2—Pulmonary Function Data of Patients Receiving Protocol 1 (Protons Only)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline (Mean, Range)</th>
<th>1 mo (Mean, Range)</th>
<th>p Value*</th>
<th>3 mo (Mean, Range)</th>
<th>p Value*</th>
<th>6 to 12 mo (Mean, Range)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L % predicted</td>
<td>1.58 (1.68–2.99)</td>
<td>1.58 (1.05–2.01)</td>
<td>NS</td>
<td>1.91 (0.97–2.65)</td>
<td>NS</td>
<td>1.85 (1.27–2.42)</td>
<td>NS</td>
</tr>
<tr>
<td>TLC, L % predicted</td>
<td>5.99 (4.43–8.75)</td>
<td>6.27 (3.24–12.10)</td>
<td>NS</td>
<td>6.65 (4.92–9.38)</td>
<td>NS</td>
<td>7.16 (4.35–13.15)</td>
<td>NS</td>
</tr>
<tr>
<td>IC, L % predicted</td>
<td>1.36 (0.76–1.89)</td>
<td>1.32 (0.83–1.91)</td>
<td>NS</td>
<td>1.29 (0.81–1.79)</td>
<td>&lt; 0.05</td>
<td>1.26 (0.60–1.88)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RV, L % predicted</td>
<td>4.17 (1.72–6.36)</td>
<td>4.64 (2.12–10.04)</td>
<td>NS</td>
<td>4.82 (3.50–7.42)</td>
<td>NS</td>
<td>5.38 (2.38–11.50)</td>
<td>NS</td>
</tr>
<tr>
<td>Raw, cm H2O/L/s</td>
<td>7.7 (1.8–22.4)</td>
<td>5.4 (0.9–14.3)</td>
<td>NS</td>
<td>5.4 (2.8–9.4)</td>
<td>NS</td>
<td>9.0 (5.9–13.7)</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1, L % predicted</td>
<td>0.54 (0.25–1.34)</td>
<td>0.80 (0.30–1.19)</td>
<td>NS</td>
<td>0.73 (0.31–1.15)</td>
<td>NS</td>
<td>0.66 (0.31–0.89)</td>
<td>NS</td>
</tr>
<tr>
<td>DLco, mL/min/mm Hg % predicted</td>
<td>7.7 (3.9–12.4)</td>
<td>10.6 (6.0–12.1)</td>
<td>NS</td>
<td>8.4 (0.9–12.8)</td>
<td>NS</td>
<td>6.7 (0.5–12.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Kco, L/min/mm Hg % predicted</td>
<td>1.7 (0.6–2.6)</td>
<td>2.5 (2.3–3.1)</td>
<td>&lt; 0.05</td>
<td>1.9 (2.3–3.1)</td>
<td>&lt; 0.05</td>
<td>1.8 (1.4–2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>62.7 (45.3–81.6)</td>
<td>66.3 (47.7–81.6)</td>
<td>&lt; 0.05</td>
<td>65.9 (47.8–72.2)</td>
<td>&lt; 0.05</td>
<td>58.9 (39.8–71.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Level of significance as compared to baseline. NS = not significant.
Dose-volume histogram analyses of patients receiving protocol 2 revealed that the 40% isodose line encompassed approximately one third of the total lung volume (median, 29%; range, 19 to 39%). In patients receiving protocol 1, the 40% isodose line encompassed a much smaller portion of the total lung volume (median, 8%; range, 5 to 14%).

**Table 3—Pulmonary Function Data of Patients Receiving Protocol 2 (Photons With Proton Boosting)**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline Mean (Range)</th>
<th>1 mo Mean (Range)</th>
<th>p Value†</th>
<th>3 mo Mean (Range)</th>
<th>p Value†</th>
<th>6 to 12 mo Mean (Range)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>2.69 (1.57–4.35)</td>
<td>2.71 (1.65–4.32)</td>
<td>NS</td>
<td>2.58 (1.65–4.29)</td>
<td>NS</td>
<td>2.38 (1.36–4.78)</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted</td>
<td>81</td>
<td>83</td>
<td></td>
<td>78</td>
<td></td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.31 (3.74–9.13)</td>
<td>6.21 (3.83–9.25)</td>
<td>NS</td>
<td>6.15 (4.23–7.54)</td>
<td>NS</td>
<td>5.25 (3.20–7.25)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>IC, L</td>
<td>2.03 (1.09–3.50)</td>
<td>1.92 (1.24–3.80)</td>
<td>&lt; 0.05</td>
<td>1.81 (1.09–3.64)</td>
<td>&lt; 0.05</td>
<td>1.59 (0.60–3.97)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RV, L</td>
<td>3.57 (1.98–7.28)</td>
<td>3.45 (1.90–6.52)</td>
<td>NS</td>
<td>3.48 (2.19–5.16)</td>
<td>NS</td>
<td>2.94 (1.41–5.77)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% predicted</td>
<td>160</td>
<td>151</td>
<td></td>
<td>155</td>
<td></td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Raw, cm H2O/L/s</td>
<td>3.8 (1.6–7.6)</td>
<td>3.4 (1.1–8.2)</td>
<td>NS</td>
<td>3.4 (1.3–5.5)</td>
<td>NS</td>
<td>5.2 (2.7–11.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.70 (1.17–2.53)</td>
<td>1.83 (1.14–2.99)</td>
<td>NS</td>
<td>1.77 (0.94–3.27)</td>
<td>NS</td>
<td>1.51 (0.84–2.96)</td>
<td>NS</td>
</tr>
<tr>
<td>% predicted</td>
<td>72</td>
<td>76</td>
<td></td>
<td>75</td>
<td></td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>DLCO, mL/min/mm Hg</td>
<td>13.0 (6.6–23.7)</td>
<td>10.9 (3.9–25.0)</td>
<td>T</td>
<td>11.4 (6.1–23.3)</td>
<td>T</td>
<td>9.5 (4.4–23.0)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% predicted</td>
<td>61</td>
<td>55</td>
<td></td>
<td>55</td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Kco, L/min/mm Hg</td>
<td>2.4 (1.0–3.9)</td>
<td>1.9 (0.9–3.2)</td>
<td>&lt; 0.05</td>
<td>2.0 (0.3–3.3)</td>
<td>&lt; 0.05</td>
<td>1.9 (1.1–3.4)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pato, mm Hg</td>
<td>71.9 (52.8–90.2)</td>
<td>74.3 (68.2–82.8)</td>
<td>NS</td>
<td>73.9 (63.9–86.5)</td>
<td>NS</td>
<td>74.2 (57.1–88.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = not significant.
†Level of significance as compared to baseline; T trend to significance, but no clear data separation on Newman-Keuls test.

**Discussion**

**Radiation-Induced Lung Damage**

Several investigators divide the clinical picture of radiation-induced lung damage into three main phases: (1) an early phase, characterized by a period of subclinical pneumonitis (first month); (2) an intermediate phase, in which acute pneumonitis supervenes (third week to several months); and (3) a late phase, in which fibrosis appears (6 months and later). To account for these phases, we selected to perform PFT testing at month 1 (early phase), month 3 (intermediate phase), and months 6 to 12 (late phase).

It is generally known that fibrosis may develop in patients without any clinical history of radiation pneumonitis. This was also the case in one of our patients. New investigation suggests that a multicellular process begins immediately after irradiation, with synthesis and secretion of numerous growth and inhibitory factors by epithelial (type II cells), endothelial cells, fibroblasts, and macrophages that precede the pathophysiologic course of both the acute pneumonitis and the late pulmonary interstitial fibrosis.

Many predisposing factors can alter the risk of developing pulmonary radiation injury. These include total dose, fraction/dose rate, lung volume irradiated, prior irradiation, chemotherapy, steroid therapy withdrawal, preexisting lung disease, and genetic predispositions.

**Radiation Therapy and Pulmonary Function**

Pulmonary function studies done on patients with lung cancer, Hodgkin’s disease, and breast cancer who underwent photon radiation to the chest show that the major impairment in function, if it occurs, is a restrictive ventilatory disorder consisting of decreases in FVC and TLC, which indicate a loss of lung parenchyma and/or stiffening of the chest wall. Decreases in FEV1 seem to be a reflection of the loss of lung volume rather than an indication of radiation-induced airway obstruction. However, the degrees of changes between preradiation and postradiation lung volume in these studies are highly variable, making such changes an insensitive marker of early radiation-induced lung damage. Of all the parameters investigated, DLCO seems to be the most sensitive and best predictive indicator of radiation-induced lung damage, thus indicating that a loss or thickening of alveolarcapillary membrane is the major factor responsible for the decline in pulmonary function.

The time course of the changes in pulmonary function seems to vary with the type of radiation injury occurring, the radiation schedules used, and the patient population studied. Emirgil and Heinemann measured pulmonary lung volumes, DLCO, and ABGs of patients who had received irradiation for breast cancer (13 patients) or lung cancer (2 patients). They found an early and progressive reduction of IC, RV, TLC, and pulmonary compliance.
Maximum breathing capacity (MBC) was similarly reduced. DLCO values were found to be reduced within 60 to 162 days.

In patients with Hodgkin’s disease, VC decreased between 1 month and 4 months after treatment and almost normalized after 12 months. FEV1 was reduced at 5 months, and DLCO showed a 20 to 60% decrease during the first 3 to 5 months.40,41

Brady and coworkers38 studied 14 patients with lung cancer in terms of change at 1 month after irradiation; most had evidence of COPD. There was a tendency toward an increased FVC following therapy, but this change, as well as changes in RV, MBC, pulmonary compliance, ABG, and maximum minute ventilation, was not statistically significant. The only statistically significant change was an approximately 15% decrease in DLCO.

Hoffbrand and colleagues37 classified patients with bronchial carcinoma undergoing irradiation into three groups: those with no history of chronic pulmonary symptoms, those with mild chronic bronchitis, and those who demonstrated severe bronchitis. Their findings included a decrease in FEV1, FVC, and DLCO following radiation, but they found no evidence that increased airway obstruction developed in patients with poor respiratory function and bronchitis.

In another study of 30 patients with bronchogenic carcinoma, Germon and Brady38 evaluated a population comprised mostly of long-term smokers with histories of COPD. The investigators showed that FVC increased at 1 month after completion of radiation therapy and then decreased progressively; functional residual capacity decreased after treatment. DLCO decreased in all but five patients at the 1-month interval; at the other intervals (3 months, 6 months, 9 months, and 12 months), the decrease was less.

Results of these studies differ only in minor details, but patient populations and protocols of the studies differed sufficiently to make comparison of results difficult. However, it appears that early-phase pulmonary function changes after conventional photon irradiation consist of an overall reduction in VC, TLC, FEV1, MBC, pulmonary compliance, and especially DLCO. These changes tend to lessen during the second or third month following radiation. There seems to be a subgroup of patients who fail to show improvement and instead develop progressive deterioration in pulmonary function. Progressive pulmonary deterioration after an initial improvement appears to develop in another subgroup.

Compared to the studies of Brady et al8 and Germon and Brady,38 patients receiving protocol 2 of our study (45.5 Gy of photons as well as 28.8 CGE of protons) showed a similar pattern: DLCO showed a trend for a decline at 1 month and 3 months and a significant decrease in the late phase. Adjusting the DLCO to alveolar volume (Kco) shows a significant decline already at 1 month but no further decline thereafter. This suggests that the decline in DLCO in the early and intermediate phases is due to thickening of the alveolocapillary membrane, but the further decline in the late phase is due to loss of lung volume. The finding that TLC along with RV showed a significant decline only in the late phase is supportive of this interpretation; VC remained unchanged.

There was no increase in bronchial obstruction as assessed by FEV1, but Raw showed a significant increase in the late phase. Since Raw, in contrast to FEV1, reflects the more central airways, this finding requires further study, especially since the central airways are more involved in the irradiation of locally advanced lung cancer than the peripheral ones. Previous studies did not measure Raw.

The patients’ subjective experience of dyspnea was unchanged at 1 month and 3 months following radiation. Interestingly, in the late phase, there was a significant increase in dyspnea even though the reduction of Kco at month 1 and months 6 to 12 were identical. It may thus be speculated that the perception of dyspnea might have been caused by increased work of breathing associated with decreased lung compliance due to pulmonary fibrosis and/or the increase in Raw. The overall change in pulmonary function was, however, not greater than in the above-mentioned studies with conventional radiation, despite a significantly higher total radiation dose, thus demonstrating the feasibility of applying higher-than-conventional doses of radiation without excess pulmonary toxicity when conformal radiation techniques with protons are used for dose boosting.

In contrast to results seen with conventional radiation, patients receiving protocol 1, for whom only protons were used to treat the tumor, experienced no decline in pulmonary function, including DLCO. The patients’ overall performance status and subjective experience of dyspnea were unchanged throughout the observation period. It appears that by utilizing conformal proton irradiation, lung function is not adversely affected despite severe preexisting pulmonary disease. In addition, it demonstrates the feasibility of applying higher-than-conventional doses per fraction, thereby significantly reducing overall treatment time.

Although the radiation dose differed in the two treatment protocols, the fractionation schedules used were considered biologically equivalent. The treatment administered in protocol 1 (proton only) utilized large daily fraction sizes (5.1 CGE). When large fraction sizes are used, the biologically equivalent dose exceeds the physical dose actually given.
CONCLUSIONS

Our observations indicate that it is feasible to apply higher-than-conventional doses of radiation at a higher-than-conventional dose per fraction without excess pulmonary toxicity when conformal radiation techniques with protons are used. Due to its demonstrated low pulmonary toxicity, dose escalation and fractionation studies are warranted to define optimal dosing schedules.

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