External beam ionizing radiation therapy (RT) has become a mainstay of treatment for neoplasms of many organs, including the lungs. Although RT benefits patients with lung cancer, exposure to RT is not without risks. RT is particularly toxic to the lungs, and it has the potential to cause fatal pneumonitis and/or fibrosis. The lungs are the major dose-limiting organs for radiation of thoracic neoplasms. The pathogenesis of radiation-induced injury to the lungs is well-understood, and therapies to attenuate the pulmonary toxicity are under exploration. However, symptomatic pneumonitis because of irradiation does not predict fibrosis, and tolerance of irradiation early in therapy does not predict the development of symptomatic pneumonitis. It is, therefore, suspected that the recognition of subclin-
clinical events, such as limited alveolitis mediated by inflammatory cells and cytokines, are important toward the treatment of pneumotoxicity.

The prompt diagnosis of radiation-induced lung injury may lead to the successful treatment of this complication of RT. Diagnostic imaging techniques have the potential to make early diagnosis of radiation-induced lung injury feasible.\textsuperscript{7,8} One example is \textsuperscript{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET). FDG-PET is most often applied in the diagnosis and staging of cancer\textsuperscript{9} but has also been found to be useful in the characterization of nonmalignant diseases.\textsuperscript{10,11} FDG-PET is an imaging modality that detects the increased uptake of glucose in areas of increased cell metabolism. The patients are injected with glucose molecules labeled with FDG. FDG uptake and concentration causes local positron emission at these sites. These positrons are instantly annihilated, producing two coplanar 511 keV photons emitted in opposite directions. These coincident and spatially opposite events are registered and imaged with a camera that can then localize the areas of increased uptake. In malignancy, the increased uptake/metabolism reflects increases in cell proliferation, blood flow, and inflammation. To determine whether increased metabolic activity occurs in nonirradiated and shielded lungs, FDG-PET was conducted before and after RT was localized to the tumor bed with shielding of the uninvolved areas. We performed a retrospective review of 16 patients with a biopsy-proven diagnosis of primary lung cancer.

Materials and Methods

This was a single-center retrospective review of 16 patients with biopsy-proven lung cancer. Three of the 16 patients (18.8%) had small cell lung cancer. Each patient received combinations of chemotherapy, RT, and surgical resection and/or biopsy between 1995 and 1999. Patients with small cell lung cancer received VP16 therapy, and patients with non-small cell lung cancer received paclitaxel and carboplatin therapy. Thoracic RT fields were designed to include the primary tumor volume and nodal groups that were at risk for regional recurrence. The initial fields were opposed anterior-posterior beam arrangements. Patients received 4,000 cGy with these initial fields. The subsequent fields were oblique and designed to exclude the spinal cord. Custom blocks were designed, fabricated, and used during all phases of the RT to minimize the normal tissue irradiation. RT was delivered concurrently with chemotherapy in a split-course schedule to minimize the toxicity. The patients received 8 consecutive days of treatment (excluding weekends), and then had 7 weekdays off, representing one 21-day cycle of therapy. RT started on day 1 of chemotherapy and concluded on day 93. FDG-PET scans were done before and after the radiation and chemotherapy. The patients were injected with FDG in doses between 8 and 15 mCi, and 45 to 60 min after the injection, imaging with a scanner (ECAT EXACT Scanner; Siemens; Munich, Germany) was performed. Scans were interpreted by a nuclear medicine physician, the nuclear medicine expert in our institution with > 25 years of experience, who was blinded to the clinical status of the patients.

Results

Following irradiation, there was tumor shrinkage in all 16 patients. In addition, 13 of 16 patients (81.2%) showed increased FDG uptake in the shielded nonirradiated lung. The pleural uptake seen in the patients exceeded the surrounding lung “background” activity by 20 to 30%. The following four patterns were recognized: (1) contralateral peripheral pleural uptake in 5 of 16 patients (31.2%); (2) ipsilateral peripheral pleural uptake in 5 of 16 patients (31.2%) [Fig 1]; (3) bilateral peripheral pleural uptake in 1 of 16 patients (6.2%) [Fig 2]; (4) bilateral diffuse background uptake in 1 of 16 (6.2%). Three patients (18.8%) showed no increased uptake in nonirradiated lung. Only one patient (6.2%) developed clinically evident radiation pneumonitis, and this patient showed bilateral diffuse uptake of FDG. The initial PET scans did not show pleural uptake.

Discussion

In 13 of the 16 patients reviewed for this study, there was increased FDG uptake after RT for lung cancer. Five patients had increased uptake in the nonirradiated lung, which was similar to the findings of previous studies.\textsuperscript{12,13} In 12 patients, these findings occurred despite the absence of a clinically evident syndrome of radiation pneumonitis. It is possible that a lymphocytic alveolitis occurred in those patients as described below. In the one patient who developed radiation pneumonitis, there was bilateral diffuse uptake on the posttreatment PET scan, including moderately increased uptake in the right lower lobe, corresponding to the field of radiation treatment, and this finding is again similar to previous reports.\textsuperscript{14} Our findings differ, however, in that the pattern of uptake in all but 1 of the 13 patients was peripheral in nature. This may indicate the presence of pleuritis, and our findings suggest that radiation-induced injury to the lung may start at the pleura. Indeed, this has been described in animal models of radiation-induced lung fibrosis.\textsuperscript{15}

Radiation-induced lung injury was first described as early as 1922,\textsuperscript{16} and the topic has been extensively reviewed in the literature.\textsuperscript{2,17–22} Classically, radiation-induced lung injury occurs in two distinct phases: pneumonitis and pulmonary fibrosis. The phase of pneumonitis is characterized by the loss of type I pneumocytes, increased capillary permeability, interstitial edema, alveolar capillary congestion, and
inflammatory cell accumulation in the alveolar space.\textsuperscript{2,3} These changes are dose-dependent, and they appear above a certain threshold level of radiation exposure. Pulmonary fibrosis is the repair process that follows the pneumonitis stage, and its underlying mechanism, extent, and time to development are still poorly understood\textsuperscript{2,3} and not obviously related to the earlier development of pneumonitis. Research\textsuperscript{2,4–6} has elucidated the role of a whole host of cytokines and tissue growth factors that are be-

**Figure 1.** PET scan demonstrating ipsilateral pleural uptake in the left lung of a patient who underwent radiation therapy and chemotherapy for lung cancer.

**Figure 2.** PET scan demonstrating bilateral pleural uptake in another patient who underwent radiation therapy and chemotherapy for lung cancer.
lieved to be involved in the development of radiation-induced lung injury, including platelet-derived growth factor and transforming growth factor-ß.

The clinical presentation of radiation-induced lung injury is extremely variable, usually developing between 2 and 6 months following the completion of RT. The initial syndrome is characterized by the insidious onset of cough and dyspnea on exertion, which can progress rapidly to severe shortness of breath at rest. A low-grade fever is common, and it may be high in severe cases. In addition, chest fullness and pleuritic chest pain may also be present. The findings of a physical examination are usually normal, but crackles and/or pleural friction rub may also be heard. In severe cases, patients may show signs of tachypnea, cyanosis, and signs of acute cor pulmonale. Radiation pneumonitis can resolve spontaneously or can progress to acute hypoxic respiratory failure, which can be fatal.

Most often, pneumonitis occurs in the field of radiation treatment, but bilateral radiation pneumonitis has been reported to occur after unilateral RT, and the reason for this is still not very well-understood. Gibson et al. studied four patients who developed radiation pneumonitis after unilateral thoracic irradiation for breast cancer, and they found an increase in the total number of cells recovered from lavage fluid in both the irradiated and unirradiated lungs. This suggested that the underlying mechanism of radiation pneumonitis is similar to that of hypersensitivity pneumonitis. Roberts et al. then performed a prospective study on women receiving RT for carcinoma of the breast who were evaluated before treatment and 4 to 6 weeks after treatment. A medical history was taken, and a physical examination, chest radiograph, quantitative gallium lung scan, respiratory function tests, and BAL were performed in these patients. They found that the patients with clinical pneumonitis developed bilateral severe lymphocytic alveolitis and bilateral increased gallium uptake, despite strict unilateral thoracic irradiation. In addition, they found that the same process occurred in asymptomatic patients without clinical pneumonitis, although the reaction was less intense in nature. The results of their second study gave additional weight to their previous suggestion that radiation pneumonitis may be a hypersensitivity reaction. Arbetter et al. reported on radiation-induced organizing pneumonitis occurring outside the direct radiation field in six patients who received RT for breast cancer. Two patients had lymphocytosis found on their BAL sample, and five patients had bronchiolitis obliterans-organizing pneumonia found on lung biopsy samples. As a result, they also suggested that radiation pneumonitis may be attributable to an immunologically mediated lymphocytic alveolitis.

More recently, Fujita et al. reported two cases of bilateral radiation pneumonitis with unilateral thoracic irradiation for lung cancer. Histologically, both patients had diffuse alveolar damage, and they found antibodies against cytokeratins 8, 18, and 19 in the patients’ sera, suggesting the possibility that autoantibodies may also play a role in the development of bilateral radiation pneumonitis.

The imaging modalities that are most often used in the diagnosis of radiation-induced lung injury are chest radiography and CT scanning. Other imaging modalities, however, have also been used, including ventilation/perfusion scanning, single photon emission CT scanning, and gallium scanning. As mentioned previously, PET scanning utilizes glucose molecules that are labeled with radioactive fluorine to detect areas of increased metabolic activity, where glucose would be preferentially taken up. The intense uptake of glucose occurs in areas with increased metabolic activity, including areas of inflammation and accelerated cell growth, such as that in malignant tumors. PET scanning, however, has also been shown to be useful in the diagnosis of nonmalignant conditions, including radiation pneumonitis. Lin et al. published a case of a patient with inoperable lung cancer who underwent a radical course of RT and chemotherapy. One month after the completion of RT, the patient developed progressive dyspnea and dry cough. Chest radiographs showed bilateral interstitial infiltrates, particularly in the left lung. An FDG-PET scan was performed as part of a research protocol, and it showed moderate diffusely increased FDG uptake in the left lung, with a sharp demarcation between the upper one third and lower two thirds, corresponding with the RT fields. The patient experienced prompt improvement after prednisone therapy was initiated.

The results described herein expand on those published by Lin et al. and demonstrate various patterns of increased lung metabolic activity in the nonirradiated lung. It is suspected that these findings demonstrate a subclinical pneumonitis, and, thus, PET scanning of the lungs in irradiated patients may provide an early demonstrable barometer of pulmonary toxicity. It must be noted, however, that increased uptake during PET scanning is not specific, because it is expected that any area of increased metabolic activity would be detected by PET scanning. Indeed, PET has been shown to be useful in the diagnosis of nonmalignant disorders, as mentioned previously. Therefore, additional prospective studies need to be conducted to verify the findings of our study. If verified, this imaging tool could prove to be useful in monitoring the patients who are receiving RT.
ing RT for thoracic malignancies and who may have predictive value for subsequent fibrosis.

References