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Impaired Permeability in Radiation-Induced Lung Injury Detected by Technetium-99m-DTPA Lung Clearance

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This study evaluates the use of the ^{99m}Tc-DTPA aerosol lung clearance method to investigate radiation-induced lung changes in eight patients undergoing radiotherapy for lung or breast carcinoma. The sensitivity of the method was compared with chest radiography for detecting radiation-induced changes in the lung, regional alterations within (irradiated region) and outside (shielded region) the treatment ports, effect of irradiated lung volume, and dependence on time after radiotherapy. **Methods:** Serial DTPA lung clearance studies were performed before the first radiation treatment (baseline), then weekly during a 5- to 7-wk course, and up to 12 times post-therapy over periods of 56–574 days. The total activity deposited in the lungs for each study was ~150 μCi (~5.6 MBq). DTPA clearance, expressed in terms of the biological half-time, $t_{1/2}$, was computed from the slopes of the least-squares fit regression lines of the time-activity curves for the first 10 min for irradiated and shielded lung regions. **Results:** Major findings include: (a) significant and early DTPA $t_{1/2}$ changes were observed in all patients during and after radiotherapy; (b) changes in DTPA $t_{1/2}$ values were observed in both irradiated and shielded lung regions in all patients suggesting a radiation-induced systemic reaction; (c) changes in DTPA $t_{1/2}$ values were correlated ($p < 0.05$) with the irradiated lung volumes; (d) significantly reduced DTPA $t_{1/2}$ values were observed in three patients who subsequently presented with clinical symptoms and/or radiographic changes consistent with radiation pneumonitis ($t_{1/2}$ fell to 19% ± 6% of baseline values, compared with 64% ± 17% in the remaining patients [$p < 0.01$]); (e) the onset of decreased DTPA $t_{1/2}$ values in these three patients occurred 35–84 days before clinical symptoms and/or radiographic changes; and (f) DTPA $t_{1/2}$ tended to approach baseline values with time after radiotherapy, suggesting a long-term recovery in lung injury. **Conclusion:** These observations show significant and early alterations in DTPA lung clearance during and after radiotherapy that may provide a sensitive assay to monitor changes in radiation-induced lung injury and may facilitate early therapeutic intervention.

Key Words: radiation-induced lung injury; radiation pneumonitis; radiotherapy; technetium-99m-DTPA; lung clearance

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Radiation-induced injury to the lungs is a potential side effect in the radiation treatment of tumors in the chest. Radiation pneumonitis presents clinically with dry cough, dyspnea and fever. Chest radiographs often reveal an infiltrate, characteristically within the radiation port. Radiation pneumonitis may subside, leaving no clinical or radiological traces, or progress slowly to irreversible chronic pulmonary fibrosis (*1,2*). Symptomatic pneumonitis and/or fibrosis occur in 5%–20% of patients irradiated for carcinoma of the lung or breast (*3,4*). Chest radiographs show that an even larger percentage of patients develop subclinical pulmonary injury (*3*).

Diagnostic procedures used previously for the detection of radiation-induced lung injury include the measurement of ^{67}Ga citrate uptake in inflammatory lung tissue (*5,6*), analysis of bronchoalveolar lavage (BAL) fluid for inflammatory cells in the lung air spaces (*7–11*), measurement of regional lung ventilation and perfusion (*12*), MR imaging (*13*), and chest radiographs (*14*) and CT scans (*15*). The usefulness and number of serial studies that can be performed are limited for each of these procedures. Gallium is limited by the high total-body radiation dose of 780 mrad (7.8 mGy) for a 3 mCi (111 MBq) dose and a 72-hr waiting time between administration to the patient and imaging. BAL is limited by trauma and discomfort to the patient; lung ventilation and perfusion measurement by the relatively high lung radiation dose of 920 mrad (9.2 mGy) for a 4 mCi (148 MBq) dose. MR imaging is limited by study cost and chest radiographs and CT scans are limited by their marginal sensitivity.

In this study, the rate of lung clearance of inhaled ^{99m}Tc-labeled diethylenetriamine pentaacetate aerosol (DTPA), a sensitive index of lung epithelial permeability (*16*), was used to measure changes in the permeability of the alveolar-capillary membrane of patients receiving radiation to the lung for treatment of lung or breast carcinomas. The method is based on the deposition of inhaled DTPA particles on the alveolar epithelial surface, followed by their diffusion through the alveolar-capillary membrane, solution in capillary blood and excretion through the kidneys. The radiation beam may cause an inflammation, thereby increasing epithelial permeability and resulting in faster DTPA clearance, expressed as a reduced biological clearance half-time, $t_{1/2}$. Conversely, the radiation beam may cause the formation of hyaline membranes and the deposition of macrophages and other cells and exudates on the epithelium, thereby lengthening the DTPA diffusion path and decreasing DTPA clearance, expressed as an increased $t_{1/2}$. The procedure is very attractive because it is noninvasive, very

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TABLE 1
Study Group

Patient no.	Age (yr)	Smoking History		Baseline $t_{1/2}$ (min)	Diagnosis	Radiation treatment		
		Type	Pack (yr)			Tumor dose (cGy)	No. of fractions	Elapsed time (days)
					Radiation pneumonitis			
2	31	Nonsmoker	—	232	Stage III-B infiltrating ductal and intraductal carcinoma, left breast	6,440	35	63
4	60	Ex-smoker	90	67	Stage III-B adenocarcinoma, right lung	6,120	33	54
5	69	Ex-smoker	72	68	Stage IV adenocarcinoma, left lung	5,720	31	56
					No radiation pneumonitis			
1	53	Ex-smoker	105	82	Stage III-B oat cell carcinoma, left lung	6,120	34	56
3	61	Ex-smoker	40	32	Stage II-A infiltrating ductal carcinoma, left breast	6,440	35	56
6	64	Ex-smoker	31	85	Stage I infiltrating ductal and intraductal carcinoma, left breast	6,100	30	44
7	67	Ex-smoker	27	39	Stage I malignant mesothelioma, left lung	4,320	24	37
8	66	Ex-smoker	40	59	Stage I infiltrating ductal carcinoma, left breast	6,100	30	44
Mean ± s.d.	59 ± 12		58 ± 31	62 ± 20		5,920 ± 685	32 ± 4	51 ± 9

sensitive and contributes a very low radiation dose of 18 mrad (0.18 mGy) for ~150 μCi (~5.6 MBq) deposited in the lungs for each study (*17*).

We hypothesized that changes in DTPA lung clearance are early indicators of radiation-induced lung injury. This study was, therefore, designed to evaluate the use of the DTPA method to investigate radiation-induced lung changes. The sensitivity of the method was compared with chest radiography for detecting radiation-induced changes in the lung, regional alterations within (irradiated region) and outside (shielded region) the treatment ports, effect of irradiated lung volume and dependence on time after radiotherapy.

MATERIALS AND METHODS

Patients

Eight patients were included in the study: four treated for lung carcinoma and four treated for breast carcinoma (Table 1). Institutional human studies review committee approval and informed consent were obtained for all patients. Seven patients were ex-smokers and one was a life-long nonsmoker. Their mean age was 59 ± 12 yr. Three of the breast carcinoma patients had lumpectomy and axillary dissection and the fourth (Patient 2) had a modified radical mastectomy before starting radiotherapy. Two lung carcinoma patients (Patients 1 and 4) and two breast carcinoma patients (Patients 2 and 3) had systemic chemotherapy before the start of radiotherapy.

Procedure

DTPA was labeled with [^{99m}Tc]pertechnetate using a multidose kit and the prescribed manufacturer's labeling procedure (Medi-Physics Inc., South Plainfield, NJ, 5 mg pentetate pentasodium and 0.17 mg $SnCl_2$). A labeling efficiency of >95% with <2.5% free pertechnetate was obtained and verified by thin-layer chromatography. Technetium-99m-DTPA aerosol (0.8 μm MMAD, 1.17 σ_g) was produced in standard medical jet nebulizers (UltraVent, Mallinckrodt, Inc., St. Louis, MO). DTPA was nebulized with a 12-liter/min oxygen flow through the nebulizer reservoir containing ~40 mCi (~1.5 GBq) ^{99m}Tc-DTPA in a volume of 2 ml saline solution.

Dynamic planar imaging studies were performed with the patients seated with their backs against a large field of view scintillation camera interfaced to a dedicated computer system. A low-energy, general-purpose collimator was used and images (128 × 128 pixels) were recorded with a 20% energy window, centered over the 140.5-keV ^{99m}Tc energy peak. Images containing 50,000–100,000 counts in both lungs were obtained during 3–5 min of tidal breathing; ^{99m}Tc-DTPA activity continued to be measured in 1-min intervals for 20 min. Each patient served as his own control and results from sequential studies were compared with the baseline values. Baseline values were also compared with results from 12 nonsmoking and 6 smoking controls from our laboratory. Serial DTPA lung clearance studies were performed before the first radiation treatment (baseline), then weekly during a 5- to 7-wk course and up to 12 times post-therapy. One hundred and thirty radioaerosol studies were conducted on the eight patients over periods of time ranging from 56–574 days. In the first two patients only, DTPA clearance also was measured after the first (200-cGy dose) and the third radiation treatments, respectively. DTPA clearance was always measured before the scheduled radiation treatment to minimize possible effects of acute radiation-induced changes.

Chest radiographs were obtained from all patients before the start and after the completion of radiotherapy and when the patients became symptomatic. Treatment planning CT scans were obtained for all patients with lung carcinoma and for Patient 2, who required chest wall irradiation after mastectomy. Changes in chest radiographs and CT scans were compared with the results of the radioaerosol studies.

All patients were treated by linear accelerator (Model SL-25, Philips Medical System, Sheton, CT) using 6-MeV photons and 10- to 12-MeV electrons. Lung carcinoma patients were initially treated with AP-PA photon fields to the tumor and regional lymphatic drainage sites, including the ipsilateral hilar region, mediastinum and, in some cases, ipsilateral and/or bilateral supraclavicular fossa. The initial dose was 4320 cGy in 180-cGy daily fractions. Additional cone-down boosting dose to the tumor was

delivered by oblique opposed fields to spare additional dose to the spinal cord. The total dose to the tumor site was 4320–6120 cGy.

The two Stage I breast carcinoma patients received treatment to the involved breast only by opposed tangential 6-MeV photon fields of 5000 cGy in 200-cGy daily fractions. This was followed by a cone-down boosting dose of 1100 cGy to the tumor bed delivered by en face 10- to 12-MeV electron field in 220-cGy daily fractions. The other two patients, with Stages II-A and III-B breast tumors, were treated with 6-MeV photons to the chest wall or ipsilateral breast, internal mammary nodal chain, supraclavicular fossa and axillary regions. The initial photon dose to these areas was 5040 cGy delivered in 180-cGy daily fractions. This was followed by a boosting dose of 1400 cGy in seven daily fractions delivered to the surgical scar of the chest wall or tumor bed by en face 12-MeV electron field. The total dose to the chest wall or tumor bed was 6440 cGy.

Data Analysis

Technetium-99m-DTPA time-activity curves of radioaerosol clearance from the lungs were obtained for ROIs placed over irradiated and shielded lung regions on each patient's gamma camera images. ROIs defining the irradiated and shielded lung regions in all lung carcinoma patients and in one breast carcinoma patient were drawn after the treatment contours from the simulation films. The ROIs of the other three breast carcinoma patients included the entire treated and shielded lungs. The contours of the posterior lung fields were set at the 20% ^{99m}Tc isocount contours of the lungs. The activity data were corrected for decay and plotted against time on a semilog scale. The time of the image with maximum lung activity was selected as zero clearance time. The rate of clearance from the lungs, defined as the slope of the regression line, was computed using a least-squares fit of the first 11 data points (10-min clearance) of the time-activity curves for each ROI. The irradiated and shielded lung regional clearance rates were expressed in terms of the biological half-times, $t_{1/2}$. No correction was made for background activity in the chest wall or pulmonary circulation because clearance calculated from data collected shortly after aerosol inhalation introduces errors of $< 10\%$ (*18*). Values of $t_{1/2}$ for each study were normalized to each patient's baseline values treated as 100% and plotted as a function of cumulative time starting with the baseline value at zero days (Fig. 1A). Half-time values $<100\%$ indicated faster clearance, while $t_{1/2}$ values $>100\%$ indicated slower clearance.

Total lung volumes were determined by summing the products of cross-sectional lung area in each CT slice and its thickness. Irradiated lung volumes were determined by manually transferring the radiation fields outlined on the simulation films to the CT slices and calculating the irradiated areas. For the three breast carcinoma patients without CT scans, the total lung volumes were estimated from the lung dimensions of the AP and lateral chest radiographs, and the irradiated lung volumes from the superimposed fields on the simulation films.

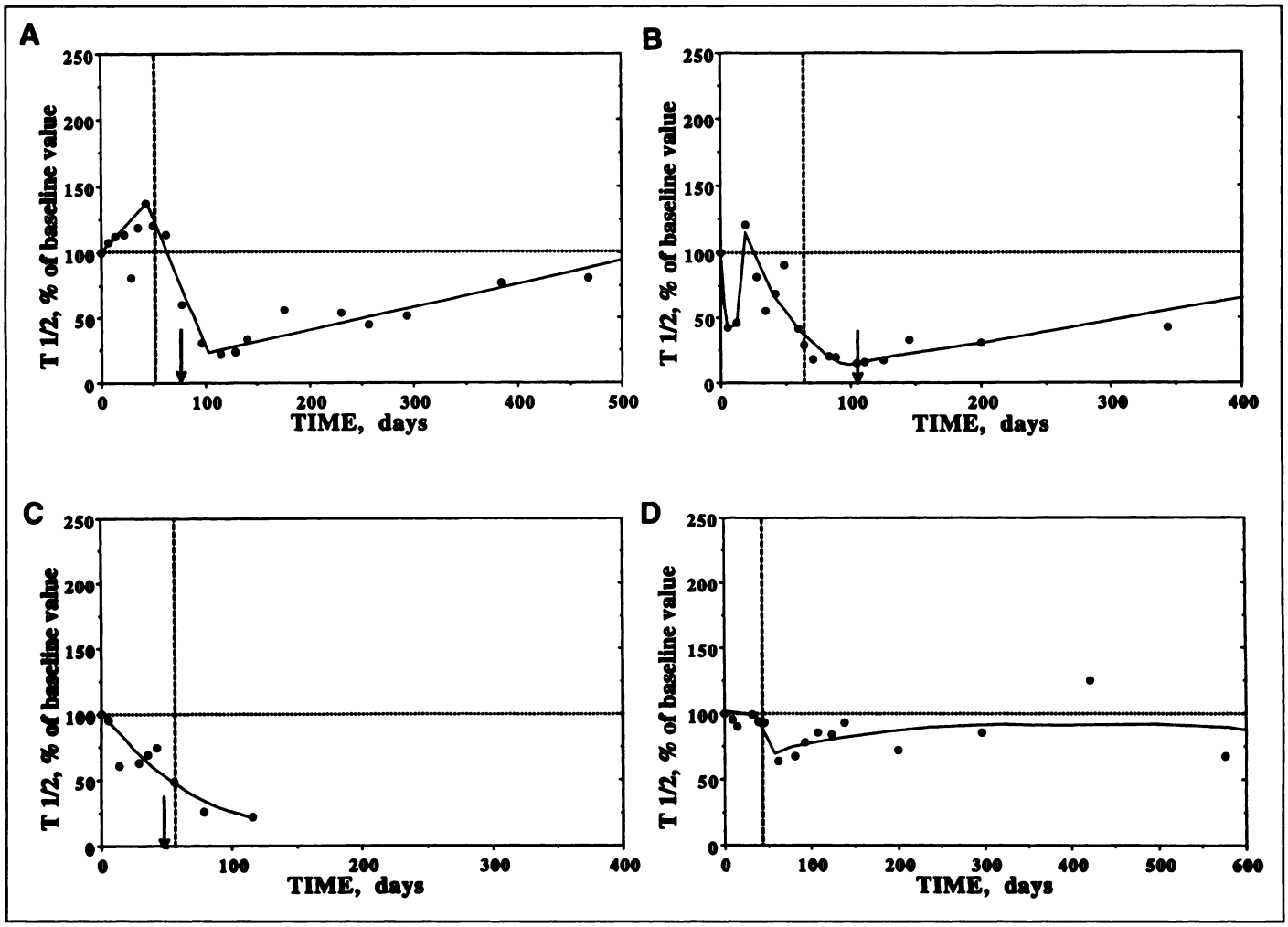

FIGURE 1. Variation of ^{99m}Tc-DTPA clearance, $t_{1/2}$, with time for the irradiated lung regions of Patients 2(A), 4(B) and 5(C), and for Patient 6(D), with no evidence of radiation pneumonitis. Note the initial $t_{1/2}$ decrease (faster clearance) and subsequent recovery in lung injury ($t_{1/2}$ increase). Dashed vertical lines mark end of radiotherapy and vertical arrows indicate time of first abnormal chest radiograph.

TABLE 2
Shielded and Irradiated Lung Volumes (% Total)

Patient no.	Minimum $t_{1/2}$ value (% baseline)	Shielded region	Radiation dose (cGy) <30,000	<4320	<5040	<6440
		Radiation pneumonitis				
2*	13	46	54	‡	18¶	—
4†	23	40	—	60	20¶	15¶
5†	22	66	—	34	12¶	—
		No radiation pneumonitis				
1†§	37	40	—	60	32¶	25¶
3*	82	85	—	—	<15	—
6*	64	90	—	—	<10	—
7†	63	50	50	26¶	—	—
8*	74	90	—	—	<10	—

*Breast carcinoma.
†Lung carcinoma.
‡Patient received combined electron and photon irradiation of chest wall.
§Patient expired shortly after completing radiation therapy, before radiation pneumonitis could be diagnosed.
¶Selected lung volumes within the radiation port received additional radiation dose.

Statistics

Observed values were reported as means ± s.d. or ± s.e.m. Analysis of variance was used to determine the statistical significance between the means of the minimum values of $t_{1/2}$, as percentage of the baseline values, for the patients with and without evidence of radiation pneumonitis. The level of statistical significance was selected at $p < 0.05$.

RESULTS

The $t_{1/2}$ baseline clearance values in the irradiated regions of the seven ex-smokers and one nonsmoker were 62 ± 20 min and 232 min, respectively (Table 1). This compares with $t_{1/2}$ values of 33 ± 18 min and 124 ± 29 min, respectively, for the smoking and nonsmoking controls previously evaluated in our laboratory (*19,20*). The results are consistent with the patients' smoking histories.

Changes in DTPA lung clearance from the baseline measurements were observed in all eight patients during and after radiotherapy, as early as after the first radiation treatment (200-cGy dose). A significant correlation ($p < 0.05$, $r = 0.73$) was obtained between the minimum value of $t_{1/2}$ and the irradiated lung volume, in other words, a larger irradiated lung volume resulted in a smaller value of $t_{1/2}$ (Table 2).

Patient 2 had changes in the chest radiographs only, while Patients 4 and 5 had clinical symptoms as well as changes in chest radiographs consistent with radiation pneumonitis. In Patient 2 had a $t_{1/2}$ that progressively decreased from 120% to 13% of baseline value between Days 19 and 103 (Fig. 1B). The patient remained asymptomatic during the entire study period, although a chest radiograph taken at Day 103 showed a mild haze over the left apex consistent with acute radiation pneumonitis, which cleared almost completely 98 days later. The half-time decreased in Patient 4 from 138% to 23% of baseline value between Days 42 and 113 (Fig. 1A). A chest radiograph taken at Day 77 showed a small area of infiltrate involving the right midlung field adjacent to the hilum. However, a chest radiograph taken 13 days later, when the patient was hospitalized with symptoms of radiation pneumonitis, showed a marked progression to radiation fibrosis with diffuse infiltration involving the right upper lobe and hilar region. In Patient 5, the $t_{1/2}$ decreased from 100% to 22% of the baseline value during the first 115 days (Fig. 1C). The patient was hospitalized for acute dyspnea at Day 46 or before the completion of therapy. Chest radiographs taken at this time showed increased markings in the right apex and perihilar area and in the left upper lobe. Another chest radiograph taken 6 days later showed that these inflammatory changes had cleared. However, a chest radiograph taken at Day 92 showed marked fibrotic changes in the right apex and left upper lobe. No changes were found in the chest radiographs of the other five patients taken after the completion of radiotherapy.

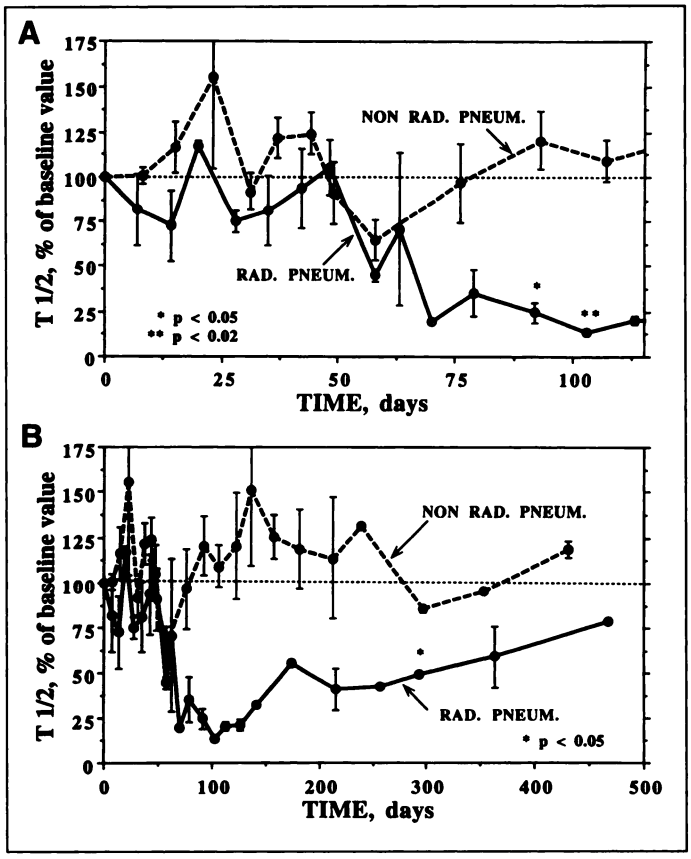

FIGURE 2. Changes in ^{99m}Tc-DTPA clearance, $t_{1/2}$, with time in irradiated lung regions of patients with and without radiation pneumonitis. Note that mean values (± s.e.m.) for the latter group are consistently larger, with spread increasing with time after radiotherapy (33–65 days). (A) First 115 days. (B) Entire study.

DTPA $t_{1/2}$ values for the irradiated lung regions of patients without radiation pneumonitis were generally >100% of baseline and consistently larger than those for the patients with radiation pneumonitis (Fig. 2). The spread increased with time after the completion of radiotherapy (33–65 days). The minimum DTPA $t_{1/2}$ values for the three patients with radiation pneumonitis were less than one-third those for the other five patients, with mean $t_{1/2}$ falling to 19% ± 6% of baseline values, compared with 64% ± 17% ($p < 0.01$) (Table 3). It took twice as long for the three patients to reach the minimum $t_{1/2}$ values, 110 ± 6 days versus 53 ± 18 days ($p < 0.01$).

Changes in DTPA $t_{1/2}$ with time in the irradiated lung regions of the patients without radiation pneumonitis closely paralleled $t_{1/2}$ in the shielded lung regions during and after radiotherapy (Fig. 3). DTPA $t_{1/2}$ values for the shielded regions of the patients with radiation pneumonitis were consistently larger than, and closely paralleled, those for the irradiated regions throughout the study (Fig. 4). However, after ~100 days the shielded regions recovered faster than the irradiated regions.

TABLE 3
Characteristics of Technetium-99m-DTPA Half-Time Curves

Patient no.	Minimum $t_{1/2}$ value (% baseline)	Time to reach minimum $t_{1/2}$ values (days)
	Radiation pneumonitis	
2*	13	103
4†	23	113
5†	22	115
Mean ± s.d.	19 ± 6	110 ± 6
	No radiation pneumonitis	
1†	37	56
3*	82	71
6*	64	59
7†	63	58
8*	74	23
Mean ± s.d.	64 ± 7	53 ± 18

*Breast carcinoma.
†Lung carcinoma.

Inspection of clearance times in smaller ROIs showed no significant differences from those obtained from the global irradiated and shielded regions.

DISCUSSION

Observations from animal studies indicate that an increase in pulmonary capillary permeability is an early effect of radiation in the lung (*21–24*). The pulmonary capillary endothelial cells appear to be an important target in the cascade of events that lead to radiation pneumonitis and/or fibrosis. Since large molecules such as albumin (molecular weight 66,000 daltons) are found in BAL fluid (*7*) more than 3 mo after the end of radiotherapy, radiation is considered to significantly increase alveolar-capillary membrane permeability. As a result, we expected to see changes in alveolar-capillary membrane permeability occurring in patients who developed radiation-induced lung injury after radiotherapy. The measurement of DTPA (molecular weight 492 daltons) lung clearance was, therefore, expected to provide a sensitive measure of radiation-induced damage (*25*).

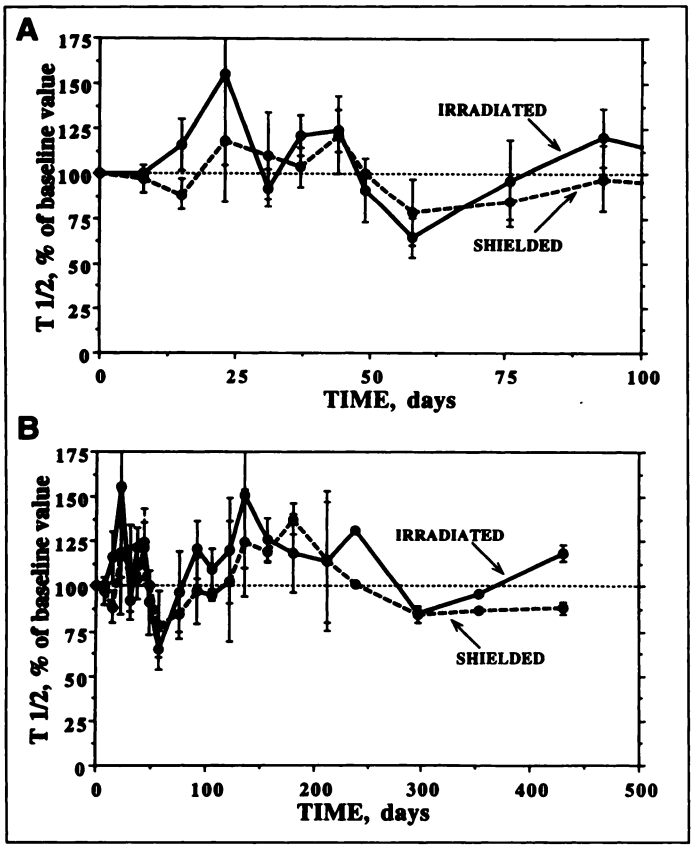

FIGURE 3. For patients without radiation pneumonitis, variations of $t_{1/2}$ (± s.e.m.) with time in irradiated lung regions closely parallel mean $t_{1/2}$ values (± s.e.m.) in shielded lung regions during and after radiotherapy (33–65 days). (A) First 100 days. (B) Entire study.

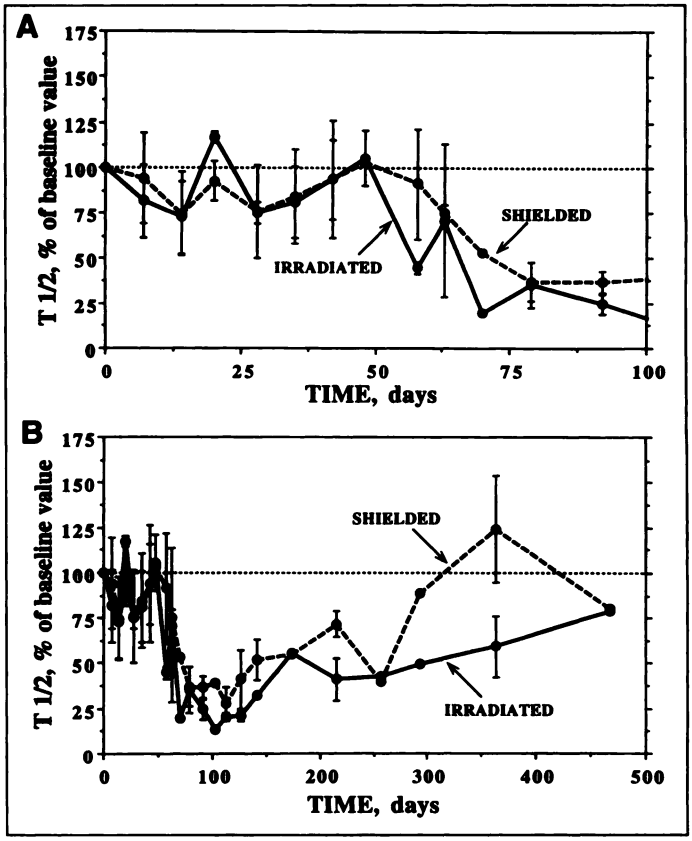

FIGURE 4. For patients with radiation pneumonitis, mean values of $t_{1/2}$ (± s.e.m.) with time in shielded regions are consistently larger than, and closely parallel, those for irradiated regions throughout study. After ~100 days, shielded regions recovered faster. (A) First 100 days. (B) Entire study.

Significant and early alterations in DTPA lung clearance were observed in all eight patients during and after radiotherapy (Fig. 2). Changes in DTPA clearance, relative to each patient's own baseline value, were found. As expected, the maximum changes in $t_{1/2}$ correlated with the irradiated lung volumes (Table 2). Three of the eight patients (Patients 2, 4, 5) had clinical symptoms and/or chest radiographic changes consistent with radiation pneumonitis. Onset of decreased $t_{1/2}$, consistent with radiation pneumonitis, was observed in these three patients 35–84 days before clinical symptoms and/or chest radiographic changes (Fig. 1). The minimum $t_{1/2}$ values ($t_{1/2}$ = 19% ± 6% of baseline) of these three patients were significantly lower, and occurred later in the study, than those of the other five patients ($t_{1/2}$ = 64% ± 17% of baseline, $p < 0.01$) (Fig. 2 and Table 3). The remaining five patients had more limited changes in DTPA clearance during the study (Fig. 1D) and showed no evidence of radiation pneumonitis. The radioaerosol procedure appeared to indicate a long-term recovery in lung injury in all surviving patients.

Our findings are consistent with the studies of Henschke et al. (*13*) and Ahmed et al. (*26*). Henschke et al. found abnormal MR images in four of 10 lung carcinoma patients beginning at 17

days after initiation of radiotherapy and a total dose of 2,000 cGy. Alterations in MR signal intensity, believed to reflect the accumulation of interstitial and intra-alveolar proteinaceous exudate and increasing interstitial cellular proliferation, were found before observation by light microscopy or radiographs and CT. The MR study, as well as ours, showed lung changes taking place much earlier in man than observed previously in radiographic or CT studies. Ahmed et al. (*26*) also found temporal variations of $t_{1/2}$, while measuring the lung clearance of DTPA in dogs exposed to single-fraction doses of 500–2,000 cGy given to one lung. Changes in DTPA clearance were observed from the second postirradiation week, as compared with abnormalities they found on CT scans and on chest radiographs at 7–8 wk.

Our results are not in agreement with the previous studies of DTPA clearance in patients treated with radiotherapy. Groth et al. (*27*) measured DTPA clearance at the end of radiotherapy and then again 3 and 12 mo later. Observed changes were small and were only seen 3 mo post-therapy, even though half the group had clinical evidence of radiation pneumonitis. Ishizaka et al. (*28*) found that DTPA clearance increased just before the onset of radiation pneumonitis in the irradiated lung, and continued to increase when clinical symptoms were already apparent. They found no clearance changes in patients who did not develop radiation pneumonitis. We cannot explain the discrepancy with our results.

The differential diagnosis of radiation-induced lung injury is based on the fact that chest radiographic changes correspond precisely with the radiation field edges. However, we observed changes in DTPA clearance both inside and outside the irradiated portals in all eight patients, suggesting a systemic reaction to the radiation (Figs. 3 and 4). Since there is often great disparity in the intensity of clinical symptoms and the degree of change visible on a chest radiograph, we suggest that the two may not be the same process. Our work suggests that the clinical factors related to radiation pneumonitis, in other words, cough, dyspnea and fever, may reflect widespread changes in the lung rather than changes confined to the radiation portal. This finding is consistent with several studies (*7–11*) that indicate radiation-induced pulmonary impairment occurs in lung regions outside the irradiated areas and suggests that the radiation may trigger an immunologically mediated mechanism, such as a hypersensitivity pneumonitis. This could result from a radiation-induced release of lung antigens or an imbalance among T-lymphocyte subsets. Studies of BAL fluid from both irradiated and shielded lung segments of patients with and without symptomatic radiation pneumonitis revealed an increased cell count with elevated percentages of lymphocytes from both lungs (*7–11*) and confirmed that an early lymphocytic alveolitis precedes the clinical and radiological appearance of radiation pneumonitis. Imaging with gallium (*5,6*) also produced an increased and bilateral lung uptake, but only in the symptomatic patients. In contrast, chest radiographs showed abnormalities only in the irradiated lungs.

CONCLUSION

Significant and early alterations in DTPA lung clearance were observed in all patients during and after radiotherapy. DTPA $t_{1/2}$ changes observed in both irradiated and shielded lung regions suggest a radiation-induced systemic reaction. Significantly-reduced DTPA $t_{1/2}$ values were observed in three patients showing clinical symptoms and/or radiographic changes consistent with radiation pneumonitis. The onset of decreased DTPA $t_{1/2}$ values was observed in these three patients 35–84 days before clinical symptoms and/or radiographic changes. DTPA $t_{1/2}$ tended to approach baseline values in irradiated and shielded regions with time after radiotherapy, suggesting a long-term recovery in lung injury. Recovery appeared greater in the shielded than irradiated lung regions of the patients with radiation pneumonitis. The observations suggest that the DTPA lung clearance method may provide a sensitive assay to monitor changes in radiation-induced lung injury and may facilitate early therapeutic intervention.

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