Effect of Radioiodine Therapy on Pulmonary Alveolar-Capillary Membrane Integrity

A.M. Samuel, T.P. Unnikrishnan, N.S. Baghel and B. Rajashekharrao

Radiation Medicine Centre and Radiation Safety Systems Division, Radiation Medicine Centre, Bhabha Atomic Research Centre, Parel, Bombay

The effects of large doses of radioiodine on the pulmonary alveolar-capillary membrane using ^{99m}Tc-DTPA clearance as an index of pulmonary damage in subjects with pulmonary metastases of differentiated thyroid carcinoma were studied. **Methods:** Technetium-99m-DTPA radioaerosols were generated by a dry aerosol generator. Data were acquired and analyzed for clearance half-time from the lungs with a scintillation camera. The study was carried out on 35 thyroid cancer patients with pulmonary metastases and on 32 patients without metastases; the results were compared to those of a control group comprising 52 subjects. The radiation dose delivered to the lungs from the therapeutic dose was calculated using MIRD methodology. **Results:** Cumulative radioiodine doses varied from 5.9 to 44.2 GBq (158–1194 mCi). The half-time clearance of ^{99m}Tc-DTPA was comparable in both patient groups and was not related to the total administered radioiodine dosage or to the radiation dose delivered to the lungs. No changes were observed for periods up to 5 yr after receiving the last radioiodine dosage. Seven patients followed at regular intervals from 6 mo to 2 yr did not show abnormal ^{99m}Tc-DTPA clearance values. One patient did show low ^{99m}Tc-DTPA clearance half-time values, which were symptomatic radiation pneumonitis. She had received a total dose of 34 GBq (922 mCi) over a 4-yr period. **Conclusion:** The incidence of pulmonary damage resulting from radioiodine therapy for lung metastases of differentiated thyroid cancer is negligible, as evidenced by the normal pulmonary clearance half-time of ^{99m}Tc-DTPA aerosols.

Key Words: alveolar-capillary membrane integrity; radioiodine therapy; thyroid cancer

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Therapeutic dosages of radioiodine given to thyroid cancer patients with pulmonary metastases may produce pulmonary damage. This complication of radioiodine therapy has been inadequately studied. Only two reports could be traced on the effects of radioiodine therapy on the lungs (*1,2*), whereas there are several reports on the effect of external radiation directed to the chest. There are many reports on clinical and histological changes of radiation-induced lung damage and the consequent radiobiological changes (*3,4*). Absorption of ionizing radiation by tissues generates highly reactive free radicals which in turn produce chemical changes and biological effects. Ionizing radiations produce more damage when tissues are oxygenated; the lungs, being highly oxygenated organs, are thus extremely sensitive to radiation (*5,6*). The expected changes in the lungs are radiation pneumonitis and fibrosis. Increased permeability of alveolar-capillary membrane and fragmentation of connective tissue produce immediate effects on pulmonary function. Late effects may also occur where destruction of basement membranes in the lungs impede reconstruction of tissue architecture and later result in functional derangement and scar formation (*6*). In our center, a large number of well-differentiated thyroid cancer patients with and without pulmonary metastases are being treated. In general, patients with pulmonary metastases require several radioiodine therapy sessions to achieve ablation of functioning lung metastases. Accordingly, they would be subjected to repeat radiation insult. Technetium-99m-DTPA (diethylenetriaminepentaacetic acid) radioaerosol clearance from the lungs has been recognized as a sensitive index of alveolar capillary membrane integrity. Several varieties of insults to the lungs have been shown to increase clearance of ^{99m}Tc-DTPA aerosols (7). This study assesses the effect of radioiodine therapy on the lungs utilizing ^{99m}Tc-DTPA aerosol clearance rates as a measure of alveolar membrane integrity. Pulmonary function tests for ventilation assessment and chest x-rays to assess any evidence of pulmonary fibrosis were also studied.

MATERIALS AND METHODS

Patient Selection

Thirty-five thyroid cancer patients with pulmonary metastases (Group 1, 14 men, 21 women, age range, 21–65 yr) and 32 patients without pulmonary metastases (Group 2, 14 men, 18 women, age range, 30–67 yr) were studied. All patients were treated by our standard protocol, which was near total thyroidectomy followed by radioiodine ablation of remnant thyroid tissue. Six months later, radioiodine therapy was given to ablate metastatic lesions which were pulmonary, nodal or skeletal. Group 1 women had no history of smoking, whereas four of the men were smokers (two to three cigarettes daily for 4–5 yr). They had stopped smoking,

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For correspondence or reprints contact: Dr. A.M. Samuel, Head, Radiation Medicine Centre, Bhabha Atomic Research Centre, c/o TMC Annexe, Parel, Bombay-400 012, India.

however, for the time period of the study (6 mo). One of these patients had unilateral metastatic disease in the lungs, 19 had bilateral diffuse radioiodine uptake and the remaining 15 had bilateral focal concentration. Of the Group 2 patients, there were only two smokers. None of the women in this group smoked.

Technetium-99m-DTPA aerosol lung clearance studies, pulmonary function tests and chest radiography were performed 6–8 mo after the last therapeutic radioiodine dose in 25 patients, 1–5 yr in 32 patients and 5–6 yr in 10 patients. These intervals were chosen to assess whether early or delayed changes occur as a result of radioiodine therapy. Seven Group 1 patients were evaluated 6–8 mo after radioiodine therapy for assessment of radiation-induced effects.

The control group consisted of 52 subjects (age range 25–60 yr) who were either volunteers working at our centre or nonsmoking subjects with no respiratory disorders.

Pulmonary Function Test

Pulmonary function testing was carried out using a microprocessor-based spiroanalyzer. During the study, the ELLIS prediction equation was used and percentage predicted values of slow vital capacity (SVC), forced vital capacity (FVC), $FEV_1/FVC\%$ (forced expiratory volume at 1 sec/forced vital capacity %), $FEV_1/SVC\%$ (forced expiratory volume at 1 sec/slow vital capacity %), maximum voluntary ventilation (MVV) and minute volume (MV) were determined (*8*). Study interpretation using ELLIS prediction equation was based on a regression equation formulated by Knudson et al. (*8*).

Technetium-99m-DTPA Aerosol Clearance Study

Labeling. A freshly prepared solution of ^{99m}Tc-DTPA was used to ensure greater than 95% labeling efficiency. DTPA cold kits were supplied by the Board of Radiation and Isotope Technology (Department of Atomic Energy, India) in lyophilized form and labeled with 555–740 MBq (15–20 mCi) of [^{99m}Tc]pertechnetate solution in a total volume of 1.0 ml.

Aerosol Generation and Administration. Technetium-99m-DTPA dry aerosols were generated using a BARC dry aerosol delivery system (*9*), which produces polydisperse dry aerosols from a concentrated ^{99m}Tc-DTPA solution by using a fine jet of compressed air (20–25 PSI) at a flow rate of 11 liters/min through a nebulizer. The aerosol droplets were of 0.8 μ size with a geometric standard deviation of 2.0. A gamma camera interfaced to a computer system was used for data acquisition and analysis. The patients inhaled the ^{99m}Tc-DTPA aerosols from the generator in the supine position and the camera's detectors were positioned to include the posterior regions of the lungs.

Data Acquisition and Analysis. The patient inhaled ^{99m}Tc-DTPA dry aerosols by tidal volume breathing for 5 min, the data were simultaneously acquired in the computer at 30 sec per frame. The total study time was 30 min (60 frames). After aerosol inhalation, the patient was given enough water to wash down any residual radioactivity in the esophagus; care was taken to ensure that the patient did not move during the study.

For data analysis, regions of interest (ROIs) were drawn over both lungs to exclude the stomach and trachea, and time-activity curves (TAC) were generated (Fig. 1). The curves were then smoothed and monoexponential fitting was carried out between peak activity and 14th frame (7 min) after the peak. Technetium-99m-DTPA clearance half-times were calculated from this exponential curve starting from peak activity of the time-activity curve. Only 7-min data were used for exponential fitting because curve characteristics change during the delayed part of the curve due to involvement of recirculation activity in the lungs and mucociliary clearance. Decay correction was not used because there was no remarkable count loss due to physical decay.

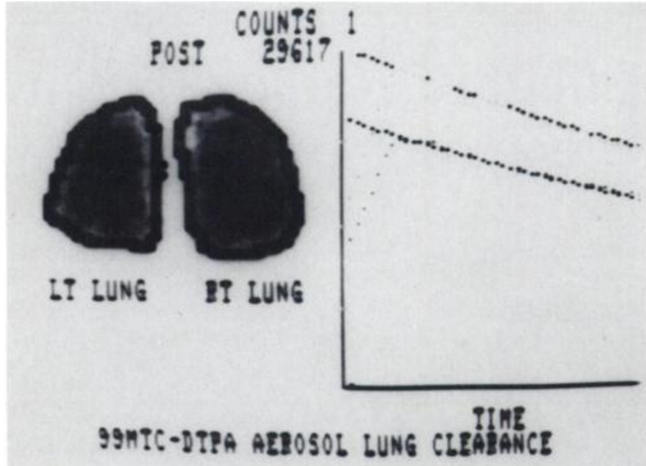

FIGURE 1. Irregular ROIs drawn over both lungs are shown. The graphs indicate the monoexponential fit between the peak and 14th frames of the time-activity curves generated over the corresponding lung ROIs. The upper and lower curves indicate time-activity curves for the right and left lungs, respectively. Both the ordinate and abscissa are plotted to a linear scale only.

Diagnostic Radioiodine Studies

All patients on follow-up were administered a diagnostic dose of 111–148 MBq (3–4 mCi) ^{131}I. Patients were off Eltroxin for 4–6 wk prior to diagnostic dose administration. Seventy-two hours later, neck images were obtained using a fast rectilinear scanner fitted with a medium-energy collimator. Radioactive iodine uptake in the neck was determined with a conventional NaI (Tl) detector system. A 120-hr whole-body profile scan was obtained using a shadow-shield whole-body counter (*10*). Any abnormal peak on the profile scan corresponding to a particular region of the body was subjected to rectilinear scanning to identify the presence of metastases. Of the 67 patients studied, 35 showed lung metastases.

Measurement of Pulmonary Radiation Dose and Biological Half-Life

To calculate the radiation dose delivered to the lungs from the administered therapeutic dose, it was necessary to measure the biological half-life of deposited radioiodine in the lungs using a portable beta gamma exposure rate meter (BGERM) (*11*). Group 1 patients were treated with ^{131}I [cumulative dosage range: 5.9–44.2 GBq (158–1194 mCi)]. No single dose exceeded 10 GBq (270 mCi). For radiation safety reasons, the patients were hospitalized in an isolation room. To determine whether an appreciable amount of ^{131}I had concentrated in lung tissue, exposure rates were measured by placing the BGERM on the posterior chest region over the left and right sides. A reading greater than the exposure rate over the thigh region (body background) indicated the presence of ^{131}I in lung tissue. Serial readings were obtained daily for 4–6 days after ^{131}I therapy. A minimum of three consecutive measurements were obtained to calculate radioiodine biological half-times in the lungs. The assumption was that there was homogeneous distribution of radioiodine in lung tissue.

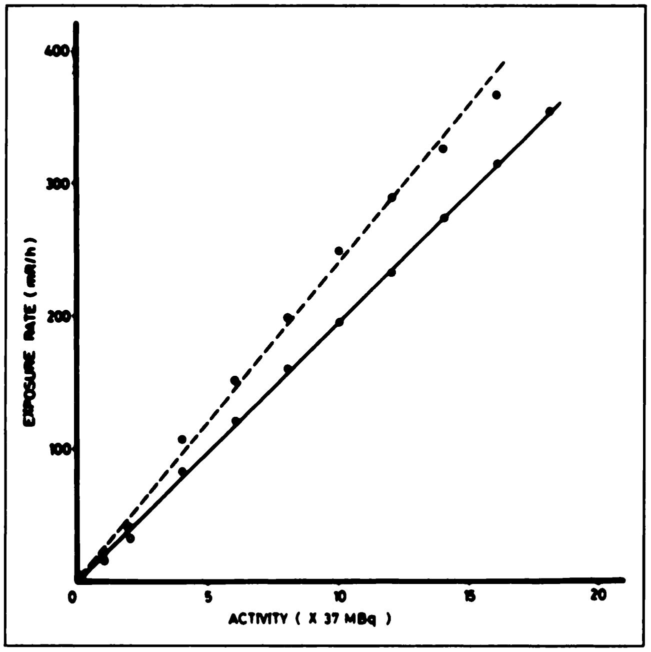

FIGURE 2. Dotted line curve indicates the ^{131}I activity exposure rate relationship for the small phantom. Continuous line curve indicates the activity exposure rate relationship for the larger phantom.

Phantom Studies for Radiation Dose Measurement

Phantom studies were obtained to establish a relationship between radioactivity concentration in the lungs and BGERM exposure rates. Two glass phantoms, 20 × 10.5 × 17.5 cm and 18 × 9 × 15 cm, were used. The glass thickness was approximately 1 mm. To simulate ^{131}I gamma ray absorption and scatter from the chest wall, both tanks were covered with 1-cm thick perspex. The size of the phantom was selected to match the dimensions of the lung as measured from chest x-rays (*12*) for patient heights ranging from 155 to 180 cm.

Radioiodine was added to the larger phantom in amounts ranging from 37 to 666 MBq (1.0–18.0 mCi); for each activity added, the surface exposure rate reading was noted. A similar procedure was used for the smaller phantom. For each phantom, a graph was plotted of the exposure rate against the amount of ^{131}I present in the phantom (Fig. 2).

For the larger phantom, a relationship was established which indicated that 37 MBq (1.0 mCi) ^{131}I in lung tissue would correspond to an exposure rate of 19 mR/hr. Similarly, for the smaller phantom, an exposure rate of 24 mR/hr was obtained. We determined that a mean exposure rate of 22 mR/hr would correspond to 37 MBq (1.0 mCi) ^{131}I in an average lung volume.

With the above relationship, radioiodine uptake in lung metastases was calculated as a percentage of the administered dose after converting the BGERM exposure rate measurement to GBq of radioiodine present in the lungs. From sequential exposure rate readings, the biological half-life of ^{131}I in lung tissue was calculated. An absorbed dose was calculated using these parameters and assuming a lung mass of 810 g. Lung mass was obtained during evaluation of dimensions of a Indian standard man by the Health Physics Division of Bhabha Atomic Research Centre (*13*). The cumulative absorbed dose to lung tissue was estimated using MIRD methodology (*14*).

RESULTS

Technetium-99m-DTPA clearance half-time values for the control subjects were 50.5 ± 17.6 min. For patients with pulmonary metastases, they were 53.2 ± 19.1 min and 49.2 ± 14.4 min for patients without pulmonary metastases. There was no significant difference between the three groups and the lower limit normal value (mean − 2 s.d.) was 25 min. One Group 2 patient had a half-time value of 23 min and two Group 1 patients had values of 21 and 11 min. All others had clearance values above the lower normal value.

DTPA clearances in both patient groups are analyzed in Table 1. The number of therapeutic doses varied from two to six over an 8–12-mo interval, and no dose ever exceeded 10 GBq (270 mCi). There was no significant difference in half-life DTPA clearance in patients receiving doses less than 7.4 to greater than 22.2 GBq (less than 200 to greater than 600 mCi).

Table 2 shows that half-time clearance of DTPA was within normal limits when total radiation dose (cumulative radiation dose of all radioiodine therapies) delivered to the lungs ranged from less than 1000 to over 5000 cGy. The majority of patients received radiation doses ≤5000 cGy.

TABLE 1
Technetium-99m-DTPA Clearance after Varying Doses of Radioiodine

	$T_{1/2}$ clearance (min)			
	74 GBq (<200 mCi) mean ± s.d.	74–148 GBq (200–400 mCi) mean ± s.d.	148–222 GBq (400–600 mCi) mean ± s.d.	>222 GBq (>600 mCi) mean ± s.d.
Group 1	50.7 ± 07.5 (n = 8)	62.4 ± 18.8 (n = 14)	55.2 ± 15.7 (n = 4)	49.3 ± 27.5 (n = 9)
Group 2	59.6 ± 16.8 (n = 12)	58.9 ± 14.3 (n = 15)	51.2 ± 15.3 (n = 3)	52.0 ± 15.3 (n = 2)
Significance level*	0.2 > p > 0.1	0.6 > p > 0.5	0.8 > p > 0.7	0.9 > p > 0.8

*There was no significant difference between Group 1 and Group 2 patients (Student's t-test).

TABLE 2
Effect of Pulmonary Absorbed Dose on ^{99m}Tc-DTPA Clearance

Controls (n = 52) mean ± s.d.	<1000 cGy (n = 9) mean ± s.d.	1000–5000 cGy (n = 13) mean ± s.d.	>5000 cGy (n = 3) mean ± s.d.
50.5 ± 17.6[a]	62.3 ± 12.1[b]	49.9 ± 19.5[c]	55.6 ± 17.0[d]

Absorbed dose calculations were feasible for only 25 Group 1 patients.
a vs. b 0.1>p>0.05; a vs. c p>0.9; a vs. d 0.7>p>0.6.

These values are much lower than the ablative radiation doses calculated for residual thyroid tissue which range from 300 to 1500 Gy and 80 Gy for ablation of nodal metastases (*15*). Radioiodine uptake in the lungs varied from 1.3% to 60% of the administered dosage, with a mean value of 10.5% ± 13.0%. The effective half-time of radioiodine in the lungs was 43.3 ± 40.4 hr. The radiation dose to the lungs varied from 120 to 16,884 cGy. Pulmonary function tests and x-ray chest findings in the majority of patients were normal. Nine patients had extensive focal, nodular bilateral disease on chest x-rays. For 14 patients, pulmonary function tests (PFT) revealed mild restrictive changes (n = 8), moderate restrictive changes (n = 3) and severe restrictive disease (n = 3). The patients with moderate and severe restrictive disease had extensive bilateral focal metastases. Only one patient developed symptoms of exertional dyspena and repeated episodes of cough with mucoid expectoration. This patient had received 34 GBq (922 mCi) radioiodine over a 3-yr period. PFT showed evidence of severe restrictive lung disease, chest x-ray showed haziness in both bases and DTPA half-time clearance was 11 min, which is suggestive of interstitial fibrosis.

Analysis of ^{99m}Tc-DTPA half-time clearance rates showed values of 58 ± 12.6 min in patients with mild restrictive lung disease (n = 8), 50.4 ± 14.1 min in moderate restrictive lung disease (n = 3) and 21.6 ± 9.2 min in patients with severe restrictive lung disease (n = 3). Patients with severe restrictive disease had faster clearance of ^{99m}Tc-DTPA: 27 and 26 min, respectively. Except for the patient with a clearance value of 11 min, these values were within 2 s.d. of lower normal values. Moreover, there was no evidence of any change in half-time clearance DTPA values in patients studied up to 5 yr after radioiodine therapy (Table 3).

Table 4 shows serial studies done in seven patients receiving varying doses of radioiodine who were observed for 2 yr. No changes in half-time clearance indicative of pulmonary epithelial damage were noted. Individual radioiodine therapy doses ranged from 2.6 to 10 GBq and the radiation dose to the lungs ranged from 130 to 16,884 cGy. Even in the patient who received 16,884 cGy ^{131}I, ^{99m}Tc-DTPA clearance was unchanged after 7 and 15 mo of therapy.

DISCUSSION

The effects of external radiation to the lungs have been well documented. The occurrence and severity of damage are semiquantitatively related to the volume of lung irradiated and the radiation dose (*16*). The development of radiation pneumonitis has been reported to vary from 20% to 100% (*17*). The mean occurrence, however, is about 41%, while late radiological changes corresponding to radiation fibrosis are reported to be about 57%–60%. In one report, radiological changes were observed in 13% of patients 3 mo, 33% 6 mo, 66% 12 mo and 100% 30 mo post-therapy. Gillman et al. (*18*) reported pneumonitis in 6% of patients. There are two consecutive phases in this syndrome: radiation pneumonitis occurring 2 to 6 mo after radiation therapy and radiation fibrosis. These phases correspond approximately to the early, intermediate and late phases of pathological changes (*19–20*). There is a 5% probability of developing clinical pneumonitis after administration of a 2650-cGy dose in 20 fractions over 4 wk to both lungs. There is a 50% probability with a 3050-cGy dose in 20 fractions over 4 wk to both lungs (*21*).

CONCLUSION

Technetium-99m-DTPA clearance of radioactive aerosols from the lungs is a well-established technique to determine the presence of pulmonary epithelial integrity (*22*). Rapid clearance values have been recorded for patients with idiopathic interstitial lung disease, for chronic smokers and for other lung diseases involving the interstitium. Data from the present study show only one incidence of radiation-induced damage to the lungs as measured by ^{99m}Tc-DTPA half-time clearance, pulmonary function tests and chest x-rays. Although the cumulative amount of ra-

TABLE 3
Comparison of ^{99m}Tc-DTPA Aerosol Clearance $T_{1/2}$ Values (min) at Different Time Intervals Following Radioiodine Treatment

	<1 yr (mean ± s.d.)	1–5 yr (mean ± s.d.)	>5 yr (mean ± s.d.)
Group 1	56.7 ± 13.7 (n = 10)	56.9 ± 19.5 (n = 19)	49.2 ± 25.1 (n = 6)
Group 2	64.8 ± 15.6 (n = 15)	53.2 ± 24.7 (n = 13)	51.3 ± 11.5 (n = 4)
Significance level	0.2 > p > 0.1	0.7 > p > 0.6	0.9 > p > 0.8

TABLE 4
Serial Patient Studies

Patient no.	Administered dose mCi (GBq)	Radiation dose (cGy) to the lungs	Time between clearance studies and therapy	^{99m}Tc-DTPA clearance ($T_{1/2}$) in lungs (min)
1	180 (6.6)	1792	6 mo	45.2
	—	—	2 yr	53.0
2	224 (8.3)	16884	7 mo	43.5
	—	—	15 mo	48.5
3	344 (12.7)	3012	1 yr	70.5
	252	296	2 yr	51.6
4	146 (5.4)	2020	7 mo	63.7
	159 (5.8)	1204	1 yr	70.8
	140 (5.2)	412	7 yr	67.0
5	260 (9.6)	—	1 yr	73.0
	—	—	2 yr	53.0
6	329 (12.2)	1312	1 yr	71.3
	—	—	2 yr	70.0
7	—	—	Pretreatment	37.3
	71 (2.6)	130	1 yr	67.4
	134 (5.0)	158	2 yr	67.9

dioiodine varied from 158 to 1194 mCi (5.8–44.2 GBq), there were no demonstrable changes, which indicate that the incidence of radiation pneumonitis as a result of internal administration is negligible and radioiodine therapy with varying doses is safe and without sequelae.

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