ACKNOWLEDGEMENTS

I would like to express my appreciation to Drs. Abass Alavi and Edward Coleman for their insightful comments and suggestions.

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Radiation Pneumonitis Imaged with Indium-111-Pentetreotide

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Early recognition of radiation pneumonitis enables adequate treatment with a reasonable chance to prevent late sequelae. The feasibility of ^{111}In-pentetreotide in detecting this condition was explored in this study. **Methods:** The degree of lung uptake of ^{111}In-pentetreotide, evaluated both visually and quantitatively by irradiated-to-nonirradiated area ratios (INIA ratio) from planar images after 24 hr, was analyzed in relation to the radiation field and compared with ventilation/perfusion (V/Q) images and chest radiographs or CT in 11 patients who had received radiotherapy to the mediastinum or to the internal mammary nodes, 10 of whom were suspected of having clinical radiation pneumonitis. Additional SPECT studies were used to map lung uptake distribution. **Results:** Indium-111-pentetreotide scans were positive in nine symptomatic patients examined 2–5 mo after radiotherapy; strongly or moderately positive in eight patients, one of whom was receiving steroid therapy without clinical response; and weakly positive in one patient with good steroid response. Indium-111-pentetreotide studies were negative in one asymptomatic patient examined 1 mo after radiotherapy and in one symptomatic patient, with subsequent diagnosis of aspecific viral pneumonitis, examined 4 mo after irradiation. Positive ^{111}In-pentetreotide scans delineated areas of radiation pneumonitis that adequately correlated with areas of decreased ventilation/perfusion and x-ray abnormalities. INIA ratios varied from 1.01 to 2.16 and, in irradiated areas with visible uptake, the lowest value was 1.29. SPECT showed lung uptake in both superficial and deep lying areas in patients with mantle irradiation fields, whereas distribution was limited to anterior areas in internal mammary lymph node chain irradiation. **Conclusion:** Indium-111-pentetreotide can detect radiation pneumonitis and may have a role in both the differential diagnosis of patients who have complaints after radiotherapy, and when supported by quantification in the monitoring of response to steroid therapy.

Key Words: radiation pneumonitis; indium-111-pentetreotide; lung uptake assessment

J Nucl Med 1996;37:584–588

In radiation therapy of the thorax, radiation pneumonitis may occur 1–8 mo after treatment, varying from mild symptoms, such as fever, dyspnea and cough, to respiratory distress (*1,2*). From 8 mo onwards, lung fibrosis may appear. Although this condition remains mostly subclinical, it may lead to progressive impairment of pulmonary function.

Early assessment of radiation pneumonitis enables adequate treatment with a reasonable chance to prevent or limit late sequelae. Treatment includes prompt and maintained use of corticosteroids, which usually results in an effective suppression of complaints associated with the above mild symptoms (*3*). A delay in the start of steroid therapy may lead to a less effective clinical response.

Recognition of clinical manifestations, together with find-

Received Apr. 3, 1995; revision accepted Jul. 29, 1995.

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TABLE 1
Patient Characteristics

Patient no.	Sex	Age (yr)	Malignancy	Radiotherapy (radiation dose, time before scintigraphy)	At time of scintigraphy: Symptoms	Steroids	Response
1	F	21	Lymphoma	Mediastinal (40 Gy, 1 mo)	No	No	—
2	F	69	Breast	Right internal mammary chain (40 Gy, 4 mo)	Yes	No	—
3	M	23	Lymphoma	Mediastinal (40 Gy, 5 mo)	Yes	Yes	Good
4	F	41	Lymphoma	Mediastinal (40 Gy, 5 mo)	Yes	No	—
5	F	53	Lung	Right Thorax (40 Gy, 4 mo)	Yes	Yes	Good
6	M	39	Lymphoma	Mediastinal (40 Gy, 5 mo)	Yes	Yes	Poor
7	F	48	Breast	Left internal mammary chain* (40 Gy, 2 mo)	Yes	No	—
8	F	66	Breast	Right internal mammary chain (45 Gy, 4 mo)	Yes	No	—
9	F	54	Lymphoma	Mediastinal† (40 Gy, 4 mo)	Yes	No	—
10	F	27	Lymphoma	Mediastinal† (40 Gy, 3 mo)	Yes	No	—
11	F	72	Breast	Left internal mammary chain (40 Gy, 4 mo)	Yes	No	—

*Preceded by chemotherapy and peripheral stem cell transplantation.
†Preceded by chemotherapy.

ings from chest radiographs, perfusion lung scans and pulmonary function tests, may help to establish an early diagnosis. Both imaging methods—chest radiography (*4,5*) and perfusion lung scintigraphy (*6–8*) with ^{99m}Tc-MAA—are useful in assessing radiation pneumonitis and functional changes of the lung after irradiation. Acute radiation pneumonitis, however, must be distinguished from other pulmonary disorders such as infection, tumor recurrence, lymphangitis etc., which, occurring in the postirradiation period, may complicate diagnostic confirmation. On the other hand, chest radiographs appear to detect abnormal changes due to acute radiation pneumonitis significantly later than other modalities (*9,10*).

Gallium-67 citrate scintigraphy also appears to be sensitive for the early detection of radiation pneumonitis (*10*). In our experience, however, normal ^{67}Ga uptake in the sternum and the thoracic spine may hamper adequate delineation of lung injury, which may limit the interpretation of images and assessment of corticosteroid response monitoring.

The sensitivity of ^{67}Ga imaging, as well as the suggestion that peptide activation in irradiated areas may be involved in the pathogenesis of lung injury (*11*), led us to explore the feasibility of imaging with the somatostatine analogue ^{111}In-pentetreotide, a marker which is widely used in oncology (*12,13*) and the treatment of granulomatous diseases (*14*) for detecting and monitoring radiation pneumonitis. We report our findings in 11 patients who received irradiation to the thorax for various malignances.

MATERIAL AND METHODS

Patients

We studied 11 patients (9 women, 2 men; aged 21–72 yr, mean age: 48 yr) who received radiotherapy to the thorax: six patients with mantle field mediastinal irradiation for malignant lymphoma, four with internal mammary lymph node chain irradiation for breast carcinoma and one with irradiation to the right hemithorax for non-small cell lung carcinoma. Radiation doses before scintigraphy and clinical characteristics are summarized in Table 1. All patients, except Patient 1, were in oncologic remission at the time of ^{111}In-pentetreotide scintigraphy. In three patients, radiotherapy was given following chemotherapy: Patient 7 received high doses of carboplatin, thiothepa and cyclophosphamide combined with autologous peripheral stem cell support for high-risk breast cancer;

TABLE 2
Scintigraphic and Radiographic Results

Patient no.	Lung uptake ^{111}In-Pentetreotide (INIA uptake ratio)*: Right anterior	Left anterior	Right posterior	Left posterior	V/Q scan abnormalities	Chest radiography/CT scan abnormalities
1	− (1.22)	− (1.18)	− (1.11)	− (1.13)	No	No
2	+++ (1.74)		++ (1.54)		Right lung (slightly)	Right upper field
3	+ (1.33)	− (1.19)	− (1.21)	− (1.10)	Both lungs	Both sides (R>L)
4	+++ (1.99)	+++ (1.94)	+++ (1.82)	+++ (1.98)	Both lungs	Both sides
5	− (1.15)	− (1.17)	− (1.02)	− (1.01)	Both lungs	Equivocal
6	++ (1.43)	++ (1.50)	++ (1.42)	++ (1.54)	Both lungs	Both sides
7		+++ (1.75)		++ (1.38)	Left lung	No
8	− (1.12)		− (1.12)		Right lung (Equivocal)	Pleural effusion
9	++ (1.37)	++ (1.29)	++ (1.39)	++ (1.34)	Both lungs	Both sides
10	+++ (1.91)	+++ (2.02)	+++ (2.15)	+++ (1.64)	Both lungs	Both sides
11		+++ (2.16)		++ (1.54)	Left lung	Left lung

*INIA ratio = irradiated-to-nonirradiated area uptake ratio.
+++ = strongly positive; ++ = moderately positive; − = negative.

FIGURE 1. (A) Anterior and posterior planar ^{111}In-pentetreotide images of Patient 4 shows intense bilateral abnormal uptake in lung areas which were included in mediastinal irradiation for a malignant lymphoma. On SPECT images (B), concentrates ^{111}In-pentetreotide uptake in both superficially and deeply located lung areas (arrows).

while Patients 9 and 10 received six and four cycles of MOPP/ABV (mechloretamine, vincristine, procarbazine, prednisone/adriamycin, bleomycin, vinblastine, respectively) according to protocols of the European Organization for Research and Treatment of Cancer (EORTC) for treatment of Hodgkin's disease (*15*).

At the time of ^{111}In-pentetreotide scintigraphy, ten patients had

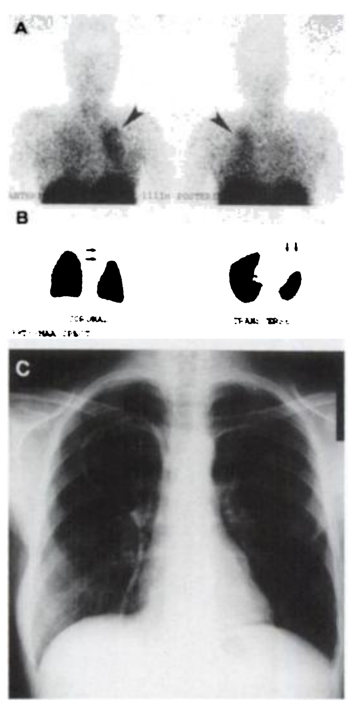

FIGURE 2. (A) Planar ^{111}In-pentetreotide images of Patient 7 with abnormal uptake in left lung (large arrows) and decreased perfusion (small arrows) on SPECT (B) indicate postirradiation changes extended to areas outside the internal mammary chain irradiation field. In contrast, chest radiography (C), performed two days before scintigraphy, shows no abnormalities.

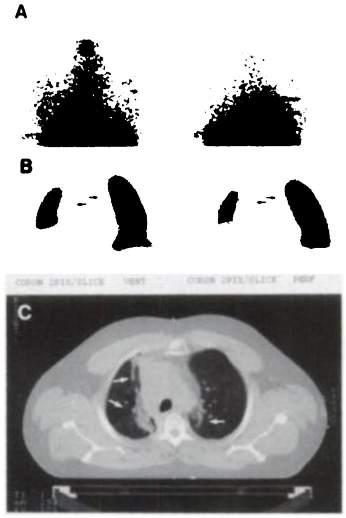

FIGURE 3. (A) Planar ^{111}In-pentetreotide images from Patient 3, performed 2 wk after start of steroid therapy, shows slightly increased uptake in medial areas of the right lung (large arrow). By contrast, decreased V/Q (small arrows) on SPECT (B) and areas of increased density corresponding to radiation portal (white arrows) on CT (C) indicate extensive postirradiation changes. V/Q and CT scans were obtained in the same week as ^{111}In-pentetreotide images.

mild symptoms, such as cough, fever and dispnea, three of whom had already received corticosteroid treatment. In two patients, follow-up studies were performed 4 wk after onset of steroid treatment.

Methods

Simultaneous anterior and posterior planar images of the thorax were obtained 24 hr after intravenous administration of 110–130 MBq ^{111}In-pentetreotide using whole-body acquisition (512 × 1024 matrix) with a dual-head gamma camera equiped with parallel-hole, medium-energy collimators and energy windows set of 172 keV and 242 keV.

The degree of lung uptake was scored visually as strongly (+++), moderately (++), and weakly positive (+) or negative (−). Irradiated-to-nonirradiated area (INIA) uptake ratios were calculated by dividing average counts per pixel from regions of interest (ROIs) drawn on planar images in lung areas which were included in the standard radiation field and in nonirradiated lung areas.

Complementary SPECT was performed in a 360° non-circular orbit (90 sec frames, 64 × 64 × 8 matrix) to map lung uptake distribution.

Ventilation (^{81m}Kr) and perfusion (^{99m}Tc-MAA) studies were performed immediately after completion of ^{111}In-pentetreotide scintigraphies.

Chest radiographs and/or CT scans were performed in the same week as the scintigraphic studies.

RESULTS

Indium-111-pentetreotide, V/Q scans and chest radiographs and/or CT scan findings are summarized in Table 2.

Planar ^{111}In-pentetreotide images were of good quality with adequate delineation of areas of radiation pneumonitis and negligible uptake in sternum, spine and thorax organs (Fig. 1). Specific uptake in possible tumor areas was not observed in any patients.

Indium-111-pentetreotide scans were strongly or moderately positive in eight symptomatic patients examined 2–5 mo after radiotherapy. One of these patients was receiving steroid therapy but was responding clinically; the other seven patients received steroid therapy after ^{111}In-pentetreotide had been performed. Indium-111-pentetreotide lung uptake correlated with decreased V/Q activity in irradiated areas; radiographic findings matched ^{111}In-pentetreotide except in two patients with negative and equivocal chest radiographs (Fig. 2), respectively.

In two patients with good steroid response, ^{111}In-pentetreotide scintigraphy was weakly positive and negative, respectively; in both patients, V/Q scans and/or chest radiographs still

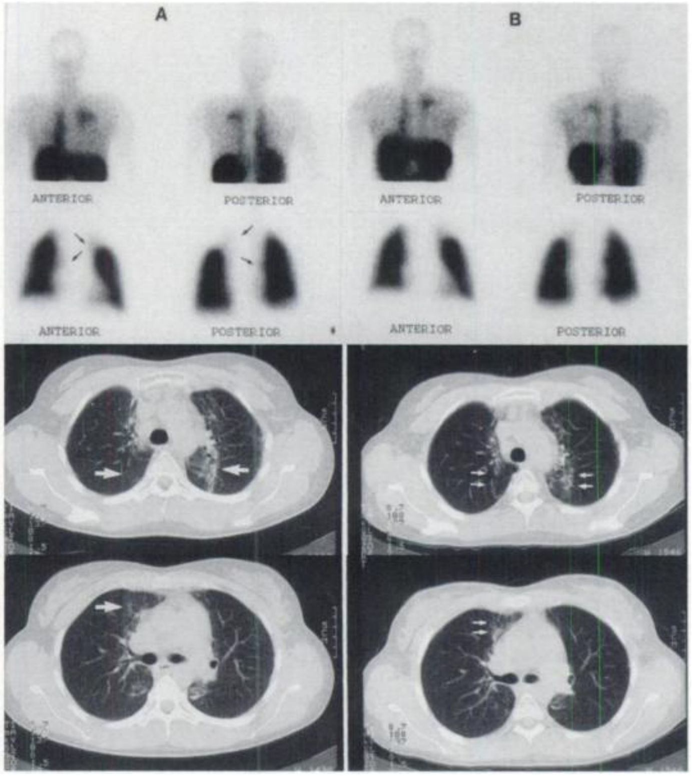

FIGURE 4. Extensive postirradiation abnormalities observed in Patient 10 before start of steroid therapy (A) include abnormal increased ^{111}In-pentetreotide uptake (top), decreased perfusion (middle, small arrows) and characteristic increased CT densities (bottom, white arrows) in both lungs with moderate improvement 4 wk after initiation of steroid therapy (B).

showed extensive abnormalities compatible with radiation pneumonitis (Fig. 3). Indium-111-pentetreotide scans were negative in one asymptomatic patient examined 1 mo after radiotherapy and in one symptomatic patient 4 mo after irradiation. In the latter patient with equivocal V/Q scan findings and pleural effusion on radiographs, the final diagnosis was aspecific viral pneumonitis. The symptoms remitted spontaneously.

INIA uptake ratios, calculated for 36 irradiated areas varied from 1.01 to 2.16; in lung areas with visible lung uptake ($n = 23$), the lowest calculated INIA ratio was 1.29 (Table 2).

Lung uptake of ^{111}In-pentetreotide in adjacent areas just outside the standard irradiation fields was found in two patients who had previously been receiving chemotherapy (Fig. 2). Areas of radiation pneumonitis mostly concerned directly irradiated lung. On SPECT, ^{111}In-pentetreotide lung uptake was observed in both superficial and deep lying areas in patients with mantle irradiation fields (Fig. 1), whereas distribution was limited to anterior areas in internal mammary chain irradiation.

In two patients, follow-up studies were performed 4 wk after starting steroid therapy. Patient 9 showed persistent ^{111}In-pentetreotide lung uptake without decrease in INIA uptake ratios, which was associated with an an unsatisfactory response to steroids; symptomatic relief and improvement of lung function were obtained only when the daily prednisone dose was increased to 25 mg. Patient 10 showed an average decrease of nearly 25% in ^{111}In-pentetreotide lung uptake after 4 wk which corresponded with CT findings and moderately satisfactory clinical response to steroids (Fig. 4).

DISCUSSION

The findings of this study show that ^{111}In-pentreotide scintigraphy is able to detect areas of radiation pneumonitis in patients with clinical manifestations. The adequate delineation of injured lung areas, which enables quantification, as well as the neglectable uptake observed in mediastinal structures suggests that ^{111}In-pentetreotide is a suitable agent for both early detection and monitoring of radiation pneumonitis. These two aspects are of importance for the clinical management of the condition which include opportune treatment with corticosteroids and objectivation of patient response in order to adjust dose.

Indium-111-pentetreotide scans of patients without steroid treatment or with unsatisfactory response correlated with V/Q lung scans showing increased uptake of the radiopharmaceutical in areas with decreased perfusion and ventilation. Abnormal areas, however, were better delineated with ^{111}In-pentetreotide planar scintigraphy, which appears to display active radiation pneumonitis better than V/Q scans. In addition, SPECT was helpful to evaluate deeply localized lung injury areas. These aspects were helpful in one case of internal mammary chain irradiation in which neither V/Q lung scan nor chest radiography were conclusive for diagnosis.

The visualization of areas of radiation pneumonitis also permitted the quantification of its uptake in relation to non-irradiated lung areas. This technique is easy and may enable more objective monitoring of clinical response to treatment with corticosteroids as performed in two patients of this series. This possibility may signify an advantage in comparison to other imaging techniques, such as CT, which was found to be very sensitive in detecting acute radiation-induced changes (*9*).

The uptake mechanism of ^{111}In-pentetreotide in areas of radiation pneumonitis remains to be elucidated. Radiation pneumonitis has been explained by early vascular alterations followed by epithelial changes and ablation of type II alveolar cells which will eventually also result in early surfactant release into the alveoli (*16*). Recently, enhanced production and release of cytokines from alveolar macrophages has been postulated as a component in the mechanism of radiation injury (*11*). The finding that uptake of ^{111}In-pentetreotide in areas of radiation pneumonitis appears to be influenced by corticosteroid treatment, as observed in some patients of this series in whom ^{111}In-pentetreotide patterns did not match the V/Q scans and x-ray findings, seems to join these assumptions.

Synergistic interaction between bleomycin and radiotherapy has been reported to enhance pulmonary toxicity (*17*) and administration of radiotherapy prior to or concomitant with bleomycin is a reason for caution (*18*). In two patients in the present study, irradiation was preceded by bleomycin chemotherapy. This may well have enhanced the pulmonary toxicity of radiotherapy. In the case of bleomycin, the pathogenesis of pulmonary injury is related to the formation of free radicals with damage of the alveolocapillary membrane, the microvasculature and type I pneumocytes included, and subsequent repair is characterized by proliferative activity of type II alveolar cells (*16,19*) which, in turn, are postulated to be the target cells in radiation injury. The strong association between the effect of chemotherapy containing bleomycin and irradiated volume was recently described in a dose-effect study of local functional and structural changes of the lung after irradiation for malignant lymphoma using ventilation-perfusion SPECT and CT (*8*).

CONCLUSION

Imaging of radiation pneumonitis with ^{111}In-pentetreotide scintigraphy appears to be feasible. Uptake of the radiopharmaceutical in injured irradiated lung areas enables quantitation and serial use of the technique. Indium-111-pentetreotide may have a role in the differential diagnosis in patients with complaints after radiotherapy and, since lung uptake appears to be influenced by corticosteroids, in the monitoring of response to therapy. In addition, the findings of this study may also be relevant for the interpretation of ^{111}In-pentetreotide studies in cancer patients investigated for tumor detection since irradiated lung areas may produce false-positive results.

ACKNOWLEDGEMENTS

The authors thank the technical staff of the nuclear medicine and audiovisual departments of The Netherlands Cancer Institute for technical support and preparing the illustrations, and Mallinkcrodt Medical B.V. for the generous supply of ^{111}In-pentetreotide.

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Measurement of Renal Function with Technetium-99m-MAG3 in Children and Adults

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A single-injection, single-sample procedure for measuring ^{99m}Tc-MAG3 clearance is presented that incorporates scaling for patient size and is valid for both children and adults. **Methods:** The procedure is based on an empirical formula in which all measurements are expressed in dimensionless combinations. The formula was obtained by fitting data collected from 122 adults and 80 children at several centers. **Results:** All results were scaled to standard adult surface area and are presented in units of ml/min/1.73 m^2. For adult subjects, the residual standard deviation (r.s.d.) calculated from a single sample at 45 min was found to be 23, using the plasma clearance calculated from a multi-sample clearance curve as a reference. This did not differ significantly from the value of 22 obtained with our previous formula, which was valid for adults only. For pediatric subjects, an r.s.d. of 24 was calculated by the new formula from a single sample at 35 min; a comparable value of 33 was found using a pediatric formula previously published. **Conclusion:** The new clearance formula is recommended as a replacement for the formula we previously published, since it is based on a larger and more diverse subject population, and since it now holds for children as well, with no loss of accuracy for adult subjects.

Key Words: kidney; technetium-99m-MAG3; radionuclide clearance

J Nucl Med 1996; 37:588–593

Received Mar. 27, 1995; revision accepted Jul. 29, 1995.

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The single-injection, single-sample technique is arguably the most accurate technique for measuring renal function that can be applied routinely in a clinical environment. We present a method for technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG3) clearance that can be used for both adults and children. It depends only on the weight of the patient and, thus, does not require making the sometimes difficult decision of whether a given patient should be classified as a child or an adult. The clearance of ^{99m}Tc-MAG3 is closely correlated with OIH clearance, which in turn is closely correlated with PAH clearance (*1,2*). Technetium-99m-MAG3 clearance thus provides a measure of renal function that can be interpreted clinically in the same way as PAH clearance or ERPF. The ERPF can be estimated by dividing ^{99m}Tc-MAG3 clearance by the factor 0.53 (*3*). At the University of Alabama Hospital, the ERPF (measured originally with OIH and currently with ^{99m}Tc-MAG3) has been used for routine monitoring of renal function for over 20 yr. Currently, it is used in more than 30 ERPF measurements each week. These measurements are performed routinely in all patients undergoing renal scintigraphy and provide supplementary information that contributes to the interpretation of the study, especially when repeated measurements are made in the same patient. The most common clinical uses are to monitor renal transplants for acute change and to monitor patients with spinal cord injury or with obstructive uropathy for progressive loss of function. Although GFR measurements can be used in the same way, they are a greater