Technetium-99m Glucoheptonate Imaging in Lung Cancer and Benign Lung Diseases: Concise Communication

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We prospectively studied technetium-99m glucoheptonate (Tc-GHA) uptake in 58 patients with newly diagnosed lung cancer and in 20 patients with pulmonary inflammatory disease or metastatic carcinoma. Fifty-three (91%) primary tumors accumulated Tc-GHA: squamous cell 20/22, adenocarcinoma 7/7, large cell 10/11, and small cell 16/18. Intensity of tumor uptake was greatest in small-cell cancer. Supraclavicular metastases were detected in two patients. Fourteen patients with mediastinal evaluation by Tc-GHA imaging and trispiral tomography underwent mediastinoscopy or thoracotomy. Five of ten patients with negative mediastinum by tomography and Tc-GHA imaging showed metastases by biopsy (false-negative Tc-GHA). Less intense accumulation of Tc-GHA was observed in 18/20 cases of pulmonary inflammatory disease or pulmonary metastases. Although Tc-GHA accumulates by an unknown mechanism in primary lung cancer, we cannot recommend its use in detecting mediastinal spread of lung cancer due to its unacceptably high false-negative rate.

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Selective uptake of certain radiopharmaceuticals by primary neoplasms of the lung permits noninvasive evaluation of metastatic spread to the hilum or mediastinum. Gallium-67 citrate (Ga-67) has been evaluated the most extensively in this capacity (*1–3*). Recently lung cancers were reported to accumulate Tc-99m-labeled glucoheptonate (Tc-GHA), in contrast to the minimal uptake by normal lung tissue or benign pulmonary conditions (*4*). This difference in uptake between malignant and benign lung diseases suggested that Tc-GHA might be more nearly specific than Ga-67 in differentiating malignant from benign processes affecting the lung. Our results show that 91% of primary lung cancers accumulated Tc-GHA intensely whereas 90% of inflammatory lesions and metastatic parenchymal lung neoplasms did so with much less avidity. We also compared mediastinal Tc-GHA imaging with mediastinoscopy and/or thoracotomy in 14 patients.

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MATERIALS AND METHODS

Fifty-eight consecutive patients with newly diagnosed lung cancer were referred to the nuclear medicine department for brain and chest imaging with technetium-99m glucoheptonate. The lung cancers were radiographically visible in all patients, and were histologically (49) or cytologically (9) proven by fiberoptic bronchoscopy or transthoracic needle aspiration. Twenty patients with radiographically visible benign lung diseases or metastases to lung were also imaged with glucoheptonate.

Scintigrams of lung and mediastinum were obtained in four views (anterior, posterior, right and left anterior oblique) 5–6 hr after intravenous injection of 20 mCi of Tc-GHA using an Anger scintillation camera (600,000 counts per image). Scintigrams were interpreted independently by two nuclear medicine specialists without knowledge of the chest films and were then compared

TABLE 1. Tc-99m GLUCOHEPTONATE UPTAKE IN 50 PRIMARY LUNG CANCERS

Cell type	No. of patients	Sensitivity (%)	Intensity (mean ± s.e.m.)
Squamous	20/22	91	2.14 ± 0.14
Adenocarcinoma	7/7	100	2.14 ± 0.26
Large cell	10/11	91	2.15 ± 0.23
Small cell	16/18	89	2.50 ± 0.15
Total	53/58	91	—

with the chest films. Intensity of tumor uptake was graded from 0–3: 0 = equal to normal lung parenchyma, 1 = equal to bone activity, 2 = equal to cardiac blood-pool activity, and 3 = equal to liver activity.

Trispiral mediastinal tomography was performed before mediastinoscopy or thoracotomy in 14 patients. Tc-GHA images and trispiral tomography were compared with the biopsy results obtained at mediastinoscopy or thoracotomy.

RESULTS

The distribution of cell types among the 58 bronchogenic carcinomas is shown in Table 1. Squamous-cell and small-cell anaplastic carcinoma were the two most frequent types. The intensity of uptake was greatest for small-cell carcinoma (2.50 ± 0.15; mean ± s.e.m.) and equally less for squamous (2.14 ± 0.14), adeno- (2.14 ± 0.26), or large-cell (2.15 ± 0.23) carcinoma, respectively. The difference in intensity of uptake between small-cell and the other carcinomas was not statistically significant ($p > 0.05$ by Student's t-test).

In addition to Tc-GHA uptake in the primary tumor and mediastinum, metastases were detected in liver (1 patient), bone (1 patient), brain (4 patients), and supraclavicular lymph nodes (2 patients). In the patient with small-cell carcinoma of the lung shown in Fig. 1, needle aspiration of the supraclavicular activity seen on the scan showed metastatic small-cell carcinoma. Metastatic squamous-cell carcinoma was also demonstrated in the second patient with a supraclavicular mass.

TABLE 2. Tc-99m GLUCOHEPTONATE UPTAKE IN CHEST LESIONS WITHOUT LUNG CANCER

Diagnosis	No. of patients
Tuberculosis	2/2
Histoplasmosis	1/1
Histoplasmoma*	0/1
Bacterial pneumonia	3/3
Radiation pneumonitis	3/3
Nonspecific interstitial pneumonitis	1/1
Lymphoma†	2/2
Metastatic carcinoma‡	3/4
Chronic eosinophilic pneumonia	1/1
Sarcoidosis	2/2
Total (%)	18/20 (90%)

* Diameter <2 cm.
† Diffuse histiocytic lymphoma 1, Hodgkin's disease 1.
‡ Primary in colon 1, parotid gland 1; malignant fibrous histiocytoma 1.

Of 20 patients with inflammatory lung disease or pulmonary metastases, 18 showed accumulation of Tc-GHA in the lesions seen radiographically (Table 2). The concentration of Tc-GHA in these lesions was generally less intense (1.69 ± 0.20) than in the patients with primary bronchogenic carcinoma. Only the difference in intensity between small-cell carcinoma and the inflammatory diseases was statistically significant ($p < 0.05$).

Figure 2 shows the chest film and Tc-GHA scintigram of a patient with a right upper-lobe mass thought to be a bronchogenic carcinoma. A transthoracic needle aspiration was nondiagnostic, and at thoracotomy the lesion was shown to be granulomatous inflammation caused by *Histoplasma capsulatum*. Although focal activity is seen in the right upper lung field on the scintigram, it is not as sharply delineated on the image as in patients with carcinoma.

Fourteen patients with Tc-GHA images and mediastinal trispiral tomography underwent mediastinoscopy

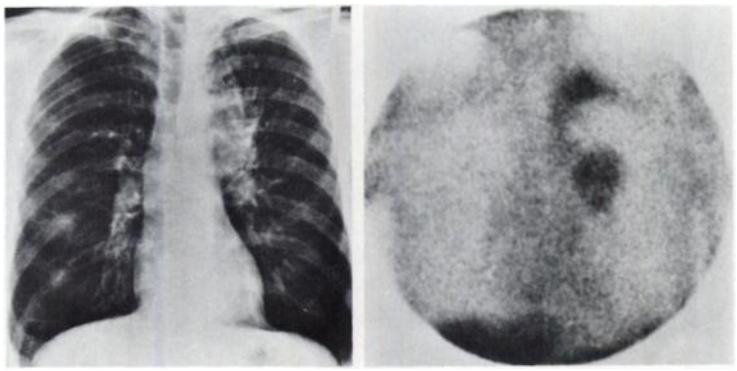

FIG. 1. Small-cell bronchogenic carcinoma. Left suprahilar mass with extension to paratracheal area (left). Tc-GHA image shows 3+ uptake by primary tumor and supraclavicular metastasis (right).

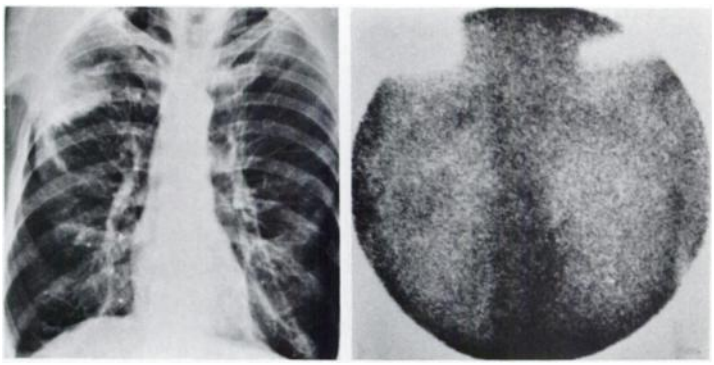

FIG. 2. Histoplasmosis. Peripheral opacity in right upper lobe (left). Tc-GHA image shows ill-defined 1+ uptake in area corresponding to opacity noted on chest radiography (right).

or thoracotomy, and the results are shown in Table 3. The remainder were inoperable due to cell type (small cell), poor pulmonary function, distant metastases, or patient refusal. Five of ten patients with negative mediastinum by tomography and Tc-GHA imaging were biopsied and were positive for metastases (false-negative Tc-GHA). In four of the five cases, the lymph nodes obtained at thoracotomy were not enlarged and metastasis could be detected by only light microscopy. In the fifth case, positive subcarinal nodes were found at mediastinoscopy in a patient with a peripheral adenocarcinoma (Fig. 3).

Of the three patients with positive mediastinum by scintigraphy and tomography, only two were found to have metastatic carcinoma at mediastinoscopy. The enlarged nodes in the third patient showed reactive sinus histiocytosis histologically (false-positive Tc-GHA).

DISCUSSION

We have demonstrated that all four cell types of bronchogenic carcinoma accumulate Tc-GHA. This confirms the findings of Vorne et al. (*4*) and expands the number of cases of adenocarcinoma, small-cell carcinoma, and large-cell carcinoma studied with this radiopharmaceutical. We were also able to show that the intensity of Tc-GHA accumulation varies with cell type. Factors that may account for the variable intensity of uptake include tumor size, central compared with peripheral location, vascular supply, and rate of cell division. Since 91% of primary lung tumors accumulated Tc-GHA, our results compare favorably with published reports of 68–96% (*2,5*) utilizing Ga-67 as the tumor-imaging agent.

In contrast to Vorne's (*4*) results, however, we found that practically all inflammatory lung lesions accumulated Tc-GHA. Patients with pulmonary and mediastinal lymphoma showed uptake of Tc-GHA. Active callus formation in a recently fractured clavicle in a patient with aspiration pneumonia was also detected with Tc-GHA.

The mechanism of Tc-GHA uptake in these diverse lesions is unknown and may be distinct in each case. Tumors may accumulate Tc-GHA because of active cellular uptake or abnormal neovascularity. GHA has a linear seven-carbon molecule structurally resembling that of glucose, and metabolically active cells may try erroneously to utilize it as a fuel (*4,6*). Tumor neovascularity may allow hyperperfusion and slow egress of Tc-GHA containing blood that would show as a focus of increased activity on the image.

With inflammatory lesions, it is possible that cells such as alveolar macrophages, polymorphonuclear leukocytes, fibroblasts, eosinophils, or lymphocytes selectively concentrate GHA. However, increased capillary endothelial permeability may allow nonspecific leakage into the lung interstitium or alveolar space (*7*). We found it particularly interesting that Tc-GHA uptake was seen in cases of interstitial pulmonary disease (sarcoidosis, chronic eosinophilic pneumonia, nonspecific interstitial pneumonitis). Bronchoalveolar lavage using a fiberoptic bronchoscope (*8*) revealed an active alveolitis in the patients with sarcoidosis (40% lymphocytes) or chronic eosinophilic pneumonia (43% eosinophils). Although Ga-67 has been used extensively to evaluate the activity of sarcoidosis (*9*) and idiopathic pulmonary fibrosis (*10*),

TABLE 3. COMPARISON OF MEDIASTINAL GLUCOHEPTONATE UPTAKE AND TRISPIRAL TOMOGRAPHY WITH RESULTS OF SURGICAL EXPLORATION*

Mediastinal biopsy	GHA+ / T+	GHA+ / T−	GHA− / T+	GHA− / T−
Tumor	2	—	1	5†
No tumor	1‡	—	—	5
Total	3	—	1	10

* Primary tumors all accumulated Tc-GHA.

† False-negative Tc-GHA image.

‡ False-positive Tc-GHA image.

Abbreviations: GHA+ = mediastinal uptake of Tc-GHA; GHA− = no mediastinal uptake of Tc-GHA; T+ = mediastinal lesion(s) by tomography; T− = no mediastinal lesion(s) by tomography.

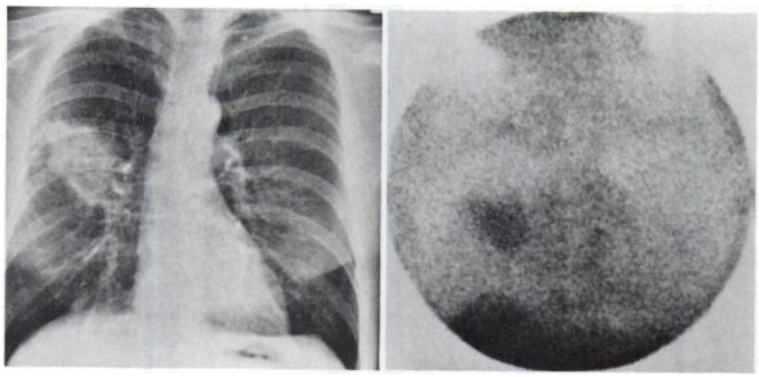

FIG. 3. Adenocarcinoma. Large lung mass radiographically separate from mediastinum (left). Tc-GHA image shows 3+ tumor uptake with negative mediastinum, but metastatic adenocarcinoma was found in subcarinal nodes (right).

we know of no reports of pulmonary Tc-GHA accumulation in these disorders.

Alazraki et al. (*1*) suggested that if the primary tumor was radiogallium-positive and the mediastinum was negative, thoracotomy should be performed rather than a staging mediastinoscopy. The data of DeMeester et al. (*2*) did not support the former conclusion because of a 33% false-negative rate for mediastinal uptake, and they recommended a staging mediastinoscopy for every patient with the same image findings as those described by Alazraki.

Preliminary results in 14 patients studied with Tc-GHA suggest that DeMeester's approach is correct. In our patients, microscopic metastases to mediastinal nodes were detected although trispiral tomography and Tc-GHA imaging were negative. Comparable studies using TCT of the chest indicate that nodes larger than 2 cm in diameter contain tumor, 1–2 cm nodes are indeterminate, and nodes less than 1 cm are rarely involved with tumor (*11*,*12*). Since a mediastinal lesion would have to be at least 2 cm to be detected by Tc-GHA, lesions 1–2 cm in size that could be biopsied at mediastinoscopy would not be detected. Clearly, chest TCT would be superior to Tc-GHA in directing the surgical staging of a patient with lung cancer.

Although Tc-GHA is avidly accumulated in primary lung cancer, we conclude that it should not be used as a means of detecting mediastinal metastases because of an unacceptably high false-negative rate. We do not know whether Tc-GHA can detect pulmonary inflammation that is not radiographically detectable, since all of the patients listed in Table 2 were included in the study because of the presence of radiographically visible lesions.

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