Thallium Scintigraphy in the Evaluation of Mass Abnormalities of the Breast

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Palpable mass abnormalities of the breast are often difficult to evaluate mammographically, especially in patients with fibrocystic change and dense breasts. The current study evaluates ^{201}Tl scintigraphy as a potential test in detecting malignancy and in differentiating malignant from benign masses. Eighty-one female patients underwent thallium scintigraphy of the breast because of palpable breast masses. An additional 30 females with no palpable breast abnormalities were also studied using ^{201}Tl. Of 44 patients with palpable breast carcinomas, 42 carcinomas (96%) were detected using ^{201}Tl scintigraphy. Three of three patients had other primary breast malignancies that were also detected. In contrast, 19 patients with palpable breast abnormalities shown on biopsy to be benign fibrocystic disease processes were not detectable on thallium studies. Of two patients with fat necrosis, none were detectable. Three of 13 patients had adenomas of the breast (23%) that were detected. The three detectable adenomas were all highly cellular. The smallest detectable carcinoma was an adenocarcinoma measuring 1.3 × 1.1 × 0.9 cm. Thallium-201 scintigraphy of palpable breast lesions is an effective test for evaluation of palpable masses. Sensitivity for detection of malignant masses greater than 1.5 cm is high. Highly cellular adenomas, however, may demonstrate significant ^{201}Tl uptake. Benign fibrocystic disease is not detectable with thallium scintigraphy. Thallium scintigraphy of breast lesions is an effective means of differentiating benign from malignant lesions.

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Women with significant clinical fibrocystic changes are typically difficult to evaluate clinically using physical palpation of the breast alone. This patient group also may be difficult to evaluate mammographically because of dense fibroglandular patterns. Even palpable cancers may not be evident mammographically in many patients (*1,2*). Mammography is known to be very accurate in examinations of fatty breasts of older women. It has been reported that the mammographic technique is less reliable for detecting lesions in the dense or dysplastic breast (*3,4*). It has also been demonstrated that treatment of palpable breast masses may be adversely affected when the clinician delays biopsy (*5,6*). Mann et al. demonstrated that a false negative mammogram may cause a considerable delay in the decision to biopsy a patient subsequently shown to have carcinoma of the breast (*1*).

Patients who are in a high risk category for the development of breast cancer (i.e., patients with a strong family history of breast cancer, patients with prior histologic evidence of cellular atypia, patients with a prior history of breast cancer who have undergone lumpectomy and radiation therapy) may be difficult to evaluate and follow mammographically because of a dense fibroglandular pattern of physical changes caused by radiation. Currently, the only established method to resolve such a dilemma is random tissue sampling which is usually attended by high nonmalignant-to-malignant biopsy ratios.

Thallium-201 has been shown to be an effective radiopharmaceutical in the detection of many types of malignancies (*7–29*). In a series of malignancies evaluated by Hisada et al., two patients were shown to have primary carcinoma of the breast detected with ^{201}Tl imaging (*10*). Sehweil et al. demonstrated that ^{201}Tl accumulated in 20 of 20 patients with primary carcinoma of the breast (*20*).

The purpose of the current study was to evaluate ^{201}Tl as a tumor-seeking agent in patients with palpable mass abnormalities of the breast. In addition, we attempted to determine sensitivity and specificity for tumor detection in a large number of patients with palpable breast abnormalities in order to determine whether thallium could be used to differentiate masses caused by malignancy from benign breast masses. The main purpose was to determine sensitivity and specificity for tumor detection and to determine whether thallium could be used to differentiate tumor benign breast masses from masses demonstrated to be malignant.

MATERIALS AND METHODS

Eighty-one female patients were referred for thallium testing because of palpable breast masses. There were no patients included in this series in which mammography demonstrated abnormalities such as calcifications or suspicious masses if a mass could not be palpated by the referring physician or a second

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physician performing the thallium examination. Biopsies were performed in all patients within 14 days of thallium imaging.

Three millicuries of ^{201}Tl were administered intravenously in the arm on the opposite side of the known breast lesion. Imaging was performed using a large field of view Anger camera. Imaging was begun 2 min postinjection and consisted of two sequential 10-min anterior chest images with the arms raised and the hands placed behind the patient's head when possible. The breasts were centered in the field of view, with the field of view extending from the mid-facial region to an area just below the dome of the liver. The initial two anterior images were followed when possible by both a right and left anterior oblique 10-min view of the affected breast with the field of view angled so as to include the axilla. Five minute marker views were done in similar positions and include markers over the nipples as well as the breast abnormality. A final 10-min anterior chest image was obtained approximately 1 hr postinjection.

In special circumstances where the right breast overlies the liver, the breast is taped in an elevated position and the camera angled to optimize the viewing of the suspected breast abnormality. In addition, the left breast may be moved and/or taped, especially on suspected breast abnormalities overlying the heart and the camera angled to optimize the view.

All studies were interpreted independently by two nuclear medicine physicians (AW and LR). A third observer (MB) was used as an arbitrator if differences existed. The only clinical history available at the time of reading was the knowledge that patients had breast masses as the basis for the study. The exception to this was the control population who underwent thallium imaging of the neck and chest for evaluation of suspected chest tumors such as thyroid cancer, lymphoma or lung cancer. The protocol in evaluating these patients was similar to the protocol for evaluating patients with breast cancer in that studies were done sequentially for 1 hr with multiple oblique views being taken. Marker views were used in the interpretation of all cases.

RESULTS

The results for ^{201}Tl sensitivity in detecting mass lesions of the breast are summarized in Table 1. Of the 47 patients with proven breast malignancy, 45 demonstrated a positive thallium study for a sensitivity of 96%. In contrast, none of the 19 patients with fibrocystic breast abnormalities demonstrate positive thallium uptake. Three of 13 patients with adenoma demonstrated increased thallium activity. The intensity of thallium uptake in these patients was similar to patients with malignancy and could not be separated scintigraphically from patients with malignancy.

TABLE 1
Thallium-201 Sensitivity in Mass Abnormalities of the Breast

	True-Positive total with disease	Sensitivity
Malignancy	45/47	96%
Primary Carcinoma	41/43	95%
Other	3/3	100%
Fibrocystic disease	0/19	0%
Fat necrosis	0/2	0%
Adenoma	3/13	23%

All three positive adenoma patients had highly cellular adenomas. Of the 34 patients with benign masses of the breast, only three had a positive test (specificity = 91%).

Normal Thallium-201 Breast Scintigraphy

The distribution of ^{201}Tl appeared homogenous throughout the breast tissue in normal patients. A normal pattern was also associated with patients who had evidence of fibrocystic change and fatty necrosis.

Figure 1 is an example of a normal patient with no known breast masses. The patient was studied because of a suspected mediastinal mass, later demonstrated to be a nonmalignant vascular structure. Note the uniform tissue background within the breast and axillary regions. The thyroid and pulmonary activity appears greatest in the initial image and fades rapidly, with almost complete clearance of the structures approximately 1 hr postinjection.

Breast Malignancy

The intensity of thallium uptake within breast malignancies presented in a narrow range, with no abnormalities noted to have activity greater than the heart. Activity greater than surrounding background activity within the breast was considered as positive. Thus, there was no attempt made to subjectively grade or quantitate an abnormal focus within the breast.

Figure 2 shows a patient with a surgically proven adenocarcinoma of the right breast. The activity in the breast abnormality is above background, but considerably less than the activity within the myocardium. Physical exami-

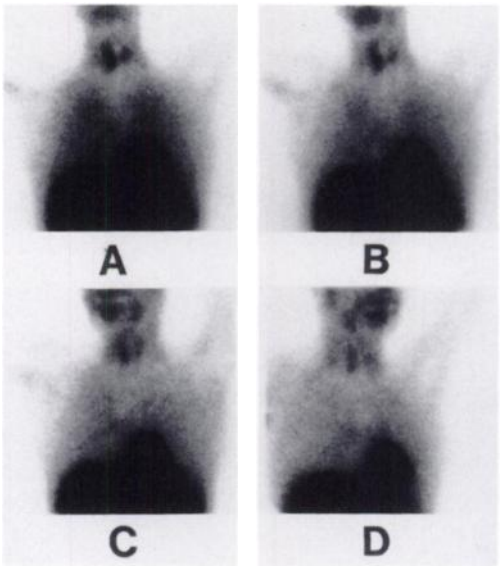

FIGURE 1. Patient with no known breast abnormalities on mammography and no mass abnormalities detected on palpation. The arms are raised to expose the axillary areas. (A and B) Anterior projections with A beginning 2 min postinjection and B beginning 12 min postinjection. (C) LAO projection of the left chest and (D) RAO projection. Note the gradual fading of the pulmonary and thyroid regions as well as the small left lobe of the thyroid.

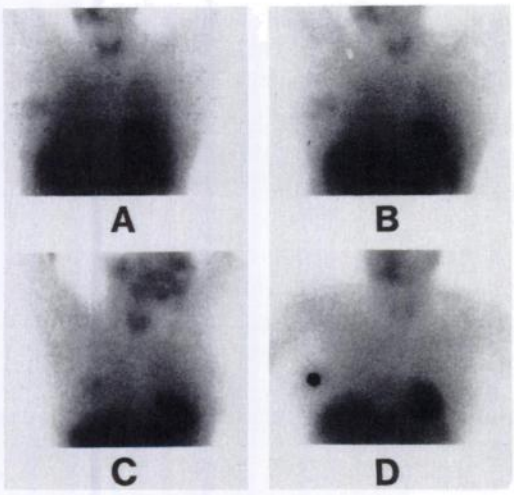

FIGURE 2. Patient with an adenocarcinoma of the right breast with no pathology found in the right axilla at the time of surgery. (A and B) Ten minute anterior projections. (C) An RAO 10-min projection with the right breast placed firmly against the collimator. Note the especially clear view of the right axilla. (D) A marker view with a thallium marker placed over the palpable lesion of the right breast.

nation demonstrated a palpable mass with no axillary adenopathy. At surgery, an adenocarcinoma of the breast was found measuring 2.3 × 1.9 × 1.7 cm.

Tumor Detectibility

The malignant breast lesions ranged in size from a tumor which measured 1.3 × 1.1 × 0.9 cm to a tumor which measured 3.2 × 3.0 × 2.4 cm. Forty patients demonstrated the tumor to be greater than 1.6 cm in maximum dimensions. Five patients had a measured maximum dimension of 1.3–1.5 cm.

Figure 3 is a patient with an adenocarcinoma of the right breast. The lesion was palpated with some degree of difficulty, but visualized well mammographically. This tumor is the smallest malignancy detected with ^{201}Tl in this series. The pathology specimen demonstrated the lesion to be 1.3 × 1.1 × .9 cm. Note the optimum tumor visualization on the 2–14 min image and rapid clearance from the tumor with poor visualization on the 14–26 min film.

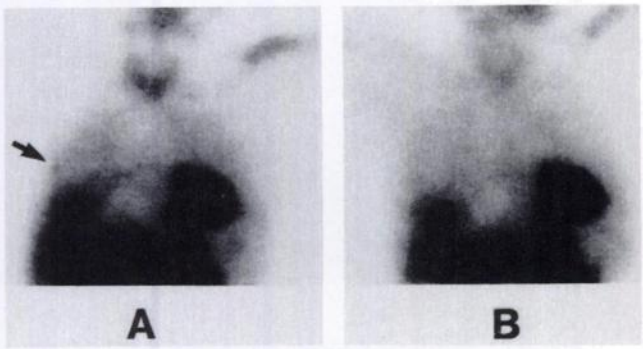

FIGURE 3. Patient with an adenocarcinoma of the right breast which was palpated with some difficulty. The lesion measured 1.3 × 1.1 × 0.9 cm on pathologic section. The axilla was negative at surgery. (A) A 10-min image beginning 2 min postinjection. (B) Image 12 min postinjection and data accumulated for 10 min. Note the fading of the lesion by the second image (B).

Detection of Axillary Metastasis

Twenty-one patients in this series were demonstrated to have axillary metastasis at the time of surgery. Of these, 12 were detected using ^{201}Tl (sensitivity 57%). Of the 12 positive patient studies for axillary metastasis, only five had palpable axillary lymph nodes.

Figure 4 shows a patient with a primary carcinoma of the left breast with three of three axillary nodes found to be positive at the time of surgery. The utility of oblique projections is shown in this patient with superior tumor localization within the breast and axilla noted on the right anterior oblique view of the left breast and axilla.

Fibrocystic Change

Nineteen patients were demonstrated to have fibrocystic change of the breast on biopsy. All of these patients presented with multiple palpable breast abnormalities, with at least one prominent area in excess of 1.0 cm. All patients within this group failed to demonstrate any ^{201}Tl accumulation. These studies were all read as normal.

Figure 5 shows a patient with a 5.0 cm firm irregular mass of the right breast with additional smaller masses in excess of 1.0 cm which were palpated bilaterally. At surgery, the large mass was found to have extensive scarring following a prior breast biopsy done 1 yr before the current study. In addition, extensive fibrocystic change was present. No thallium activity was noted within this large mass or remaining breast tissue.

A region of increased uptake to the right of the heart near the midline in this patient is similar to uptake noted in 30%–40% of all patients studied with ^{201}Tl. It is felt to

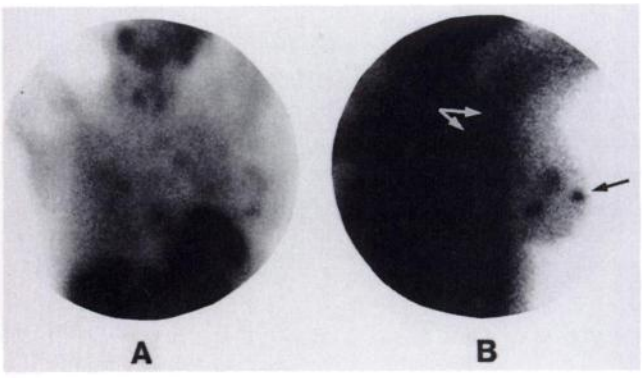

FIGURE 4. Patient with an adenocarcinoma of the left breast. The thallium study demonstrates increased activity in at least two foci within the left breast as well as axillary adenopathy both on the anterior as well as RAO projection of the left breast and axilla (B). The axillary nodes (white arrows) are outlined by the relatively low activity within the axilla. The nipple marker is demonstrated by the black arrow while the left breast demonstrates two discrete areas of tumor.

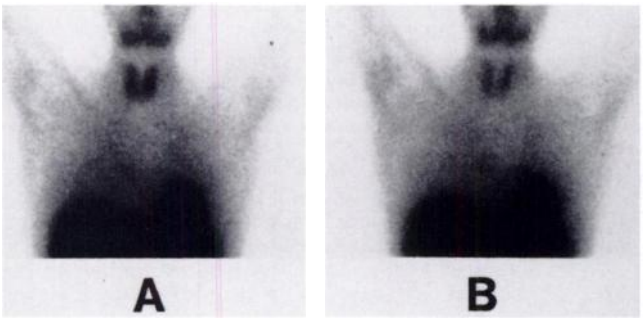

FIGURE 5. Patient with known fibrocystic disease who underwent breast biopsy one year prior to this study. Ten-minute images begun 2 min postinjection of the anterior chest (A and B) demonstrate no abnormal accumulation despite a 5.0 cm right breast mass which was firm and irregular to palpation. At surgery, the patient was found to have a large connective tissue scar as a reaction to a prior biopsy. Extensive fibrocystic disease was also present and there was no evidence of carcinoma.

be normal uptake in the region of the superior venacava and right atrium.

Controlled Population

Thirty patients with no palpable breast abnormalities were included in the series. These patients were referred for evaluation of other potential tumors, and were studied with imaging protocols similar to those studied for breast cancer, with the exception of no marker views and oblique views limited to the right anterior oblique view of the right breast and left anterior oblique view of the left breast. There were no false-positive readings within this patient group (specificity = 100%).

DISCUSSION

Thallium-201 is thought to behave similarly to potassium biologically (*30–33*). Possible mechanisms for uptake into tumor cells include the action of the ATPase sodium-potassium transport system in the cell membrane which creates an intracellular concentration of potassium greater than the concentration in the extracellular space (*34*). Thallium is thought to be influenced significantly by this system in tumors (*35,36*). In addition, a co-transport system has been identified which also is felt to be important in uptake of thallium by tumor cells (*36*).

Ando et al. determined that the biodistribution of thallium in animal tumor models was strongly influenced by tumor viability (*37*). Tumor uptake in humans has also been shown to be related to viability (*14,25*). Blood flow to the tumor tissue appears important for purposes of delivery (*8,14,33,35*). Cell characteristics such as tumor type or tumor grade may also influence thallium uptake in several tumors (*14,17,22,23,27*).

The rationale for multiple sequential images of the breast was based upon the observation that thallium distribution changes over time in many organs.

Initially, there is a high degree of concentration in the thyroid occurring within a few seconds postinjection. This fades gradually over a 1 hr period. Pulmonary background activity is also higher on the initial images, as is the general soft-tissue uptake. All of the breast tumors were observed on the initial 10 min image which was started 2 min postinjection. In addition, the tumors were visible throughout the study including the final image which was completed approximately 1 hr postinjection. Subjectively, the optimum time for observation appeared to be 15–45 min postinjection, and corresponded to reduction in soft-tissue and pulmonary activity. In one instance, the tumor was best seen on the initial 10-min image and appeared to fade rapidly with the delayed views (Fig. 3). This was an unusual circumstance and not generally observed in the study.

The use of multiple views gave a greater degree of confidence in the reading of breast abnormalities. The oblique views seem to give more information with respect to the axillary areas.

The current study demonstrates a high sensitivity for thallium in palpable breast malignancies. In 47 palpable breast malignancies, only two were not detected with ^{201}Tl. Both were adenocarcinomas of the breast. One tumor was a 2.0 × 1.8 × 1.8 cm tumor deep within the breast in a patient with a large pendulous breast. The other tumor not detected was a 1.6 × 1.5 × 1.5 cm tumor located in the high posterior superior tail of the breast tissue adjacent to the axilla. The smallest lesion detected was a 1.3 × 1.1 × 0.9 cm tumor (Fig. 3). Our findings are in agreement with Sehweil et al. demonstrating an extremely high sensitivity for detecting palpable carcinoma of the breast (*25*).

Patients referred to the study because of palpable breast masses and found to have fibrocystic changes pathologically with no evidence for tumor or adenoma failed to demonstrate abnormal thallium activity. The results in this population were similar to the control group in which no palpable breast abnormalities were evident. Of the 19 patients with adenomas of the breast, 16 were considered entirely normal. Three patients showed significant activity within the adenoma and all three demonstrated highly cellular adenomas. The intensity of uptake in the three adenomas was in the same narrow range as the carcinomas and could not be differentiated from a malignant lesion.

In two patients demonstrated to have fat necrosis as the basis for the mass abnormality of the breast, no abnormal thallium activity could be demonstrated.

Mammography has been shown to be an imperfect test for detecting breast carcinoma. Mann et al. examined 165 patients with palpable breast masses that were determined to be malignant. Of the 165 patients, 105 had mammography during their initial examination. Thirty-six patients were found to have false-normal mammograms (34.2%).

When biopsies were performed within 2 mo of the false-negative mammograms, 17.6% of the patients had axillary node involvement. When the biopsies were delayed from 3–24 mo, there was a threefold increase in the number of patients with abnormal nodes. Mann as well as other

investigators have determined that delays in diagnosis and treatment may be associated with an increase in advanced disease (*36–38*). This group concluded that mammography had certain limitations particularly in young women with dense breasts.

Holland et al. evaluated patients with mammographically occult breast cancers (*2*). In this series, five patients had invasive ductal carcinoma and five patients had invasive lobular carcinoma. The mean diameter of the five mammographically occult invasive ductal carcinomas was 2.0 cm, while the mean size for the mammographically occult invasive lobular carcinomas was 5.0 cm. This group felt that invasive ductal carcinomas are mostly associated with a strong desmoplastic reaction, but if the tumor is imbedded in dense fibroglandular tissue the difference in density may not be enough to be appreciated mammographically as a focal mass. This group also found that invasive lobular carcinoma in dense breasts can obtain a size of several centimeters and may still lack mammographic signs.

In patients with a high risk for the development of breast cancer and who have mammograms considered difficult to interpret, a thallium study may help to determine which patient population should be evaluated surgically.

The data indicate that the use of thallium can potentially define a population of patients in whom the presence of a positive test would justify an immediate biopsy due to the high specificity for carcinoma. The presence of a negative thallium breast study is highly suggestive of benign etiologies for palpable breast masses since the sensitivity for carcinoma in this group is high (96%).

Thallium-201 appears to be highly sensitive for the detection of breast malignancy in palpable breast masses and insensitive for the detection of benign abnormalities with the exception of highly cellular adenomas. These characteristics may be useful clinically when there is a need to differentiate a benign from a malignant process in patients with palpable breast lesions and suggest a rationale in selecting patients for biopsy.

ACKNOWLEDGMENTS

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SELF-STUDY TEST

Pulmonary Nuclear Medicine

Questions are taken from the *Nuclear Medicine Self-Study Program I,* published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 70.

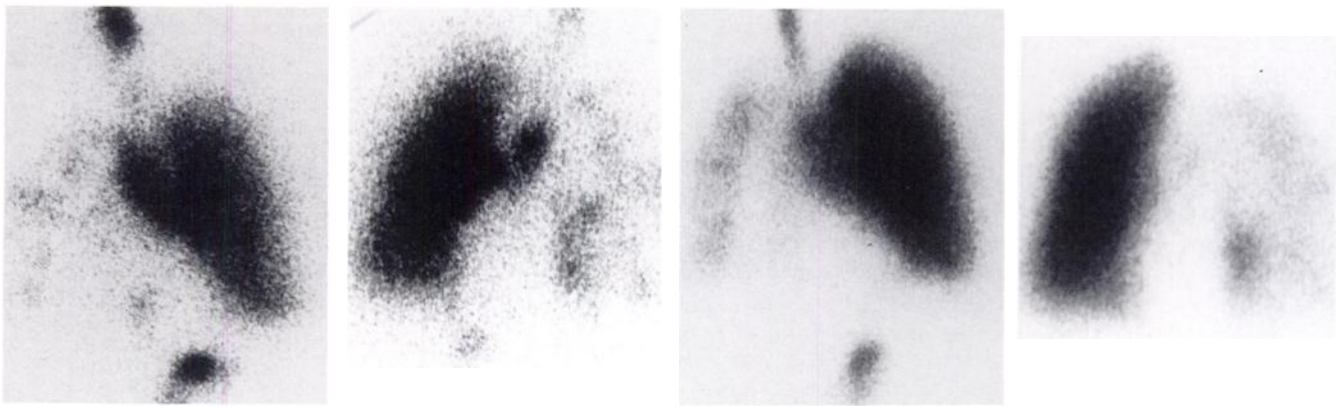

FIGURE 1.

The ^{99m}Tc DTPA aerosol and ^{99m}Tc MAA perfusion images shown in Figure 1 were obtained from a 65-yr-old woman who had increasing shortness of breath. The aerosol images (each 100,000 counts requiring about 150 sec of imaging time) were obtained immediately before the perfusion images (each 400,000 counts requiring about 60 sec). True statements concerning these images include:

1. The central airways deposition indicates that the aerosol droplets were too large to penetrate into the periphery of the right lung.
2. The medial right lower lobe activity seen on the perfusion image probably is "shine-through" from right lower lobe aerosol deposition.
3. The scintigraphic findings are typical of those seen in patients who have undergone irradiation of the right hemithorax for lung cancer.

True statements regarding sarcoidosis include:

4. It is a systemic disorder associated with abnormalities of the immune system's response to an infectious agent.
5. Most patients with sarcoidosis develop progressive deterioration in pulmonary function as a result of extensive pulmonary fibrosis.
6. The pathologic finding in the lungs of patients with early sarcoidosis that is most directly related to pulmonary ^{67}Ga uptake is alveolitis with granuloma formation.
7. Pulmonary function tests generally show progressive deterioration of lung reserve in patients with normal ^{67}Ga pulmonary scintigrams.
8. The magnitude of ^{67}Ga uptake in the lungs of patients with sarcoidosis has been shown to correlate with both the severity of pulmonary function abnormality and the radiographic severity of pulmonary fibrosis.

(continued on page 70)