A Complementary Role for Thallium-201 Scintigraphy with Mammography in the Diagnosis of Breast Cancer


From the Section of Nuclear Medicine, Department of Radiology; Section of Surgical Oncology, Department of Surgery; Section of Oncology-Hematology, Department of Medicine; Boston City Hospital, Boston University School of Medicine, Boston, Massachusetts

Physical examination and mammography are currently the only proven and reliable methods of early detection of breast cancer. Although both procedures are highly sensitive, their limited specificity often requires surgical biopsy in order to differentiate between malignant and benign lesions. The purpose of this prospective study is to investigate the diagnostic specificity of thallium imaging for breast cancer and to determine its efficacy as a complement to mammography. Two groups were studied: Group A: Patients found to have breast abnormalities and scheduled for biopsy or surgery and Group B: Patients who were suspected to have a recurrence of cancer after mastectomy or lumpectomy. In Group A, thallium scans of 32 breasts in 30 patients were performed prior to biopsy or surgery, yielding pathological diagnoses of 31 breasts in 29 patients. Results for Group A included seven true-positive thallium scans, twenty-two true-negative scans, two false-negative scans, and one false-positive scan. In Group B, seven patients were scanned to evaluate subcutaneous nodules for breast cancer following mastectomy or lumpectomy. Results for Group B included five true-positive scans, one true-negative scan, one false-negative scan and no false-positive scans. Thallium scanning was shown to have high specificity for cancer (specificity 96% and sensitivity 80%), suggesting that this technique should be evaluated in additional patient studies to determine its role in clinical situations.

J Nucl Med 1993; 34:2095–2100

Breast cancer is one of the most commonly occurring cancers among women in North America. Current statistics show that one in nine women in the United States will develop breast cancer at some time during her life. Patient prognosis has been shown to improve with early detection and aggressive treatment (1–4). Today, early detection relies on patient self-examination, physician physical examination and radiographic mammography. In addition, mammography is currently the only reliable method to detect nonpalpable breast cancer (5–10).

The well known major radiographic signs for cancer, either a dominant or spiculated mass with microcalcifications, are not 100% specific, representing a significant limitation of mammography. Benign conditions, such as post-traumatic hematoma, fat necrosis or abscess, may demonstrate these signs. Alternatively, some breast cancers may not present with a dominant or spiculated mass, thus simulating benign lesions on mammography (11–17). The problem of limited specificity of mammography is especially marked when only the "indirect signs" are present. These "indirect signs" include asymmetric breasts, focal architectural distortion, microcalcification without mass and ductal asymmetry. Statistically, only a small percentage of these mammographic findings are caused by malignancy (18–25).

There is controversy among experts as to whether the presence of indirect signs alone is grounds for biopsy. In the event that mammography detects a localized abnormality without the pathognomonic signs of benignity, the patient and her physician have only the limited management options of either prompt excision, aspiration for histology, or short-interval follow-up mammography to detect growth (18–25). In practice, a true-positive biopsy rate of 10–30% has been accepted for lack of more specific diagnostic alternatives (3,23–26). One alternative, ultrasonography, is useful only in a small percentage of cases in which the lesions are cystic (27). Clearly, there is a great need for the development of new and reliable methods for diagnosis of breast cancer to complement the existing diagnostic procedures of palpation, mammography and ultrasonography.

In the past, scintigraphy employing the use of radiotracers, including 99mTc-pertechnetate, 99mTc-labeled phosphates and gallium, had been tested for breast cancer evaluation based upon the theory of increased avidity in malignant lesions. However, a number of benign breast lesions also demonstrated high avidity for these radiotracers, rendering them unsuitable for clinical use. In 1987, theoretical factors and empirical data led us to conceive the

Received Nov. 4, 1992; revision accepted Aug. 5, 1993.
For correspondence or reprints contact: V. W. Lee, 10 Mohawk Dr., Framingham, MA 01701.
idea of using $^{201}$Tl for breast imaging. Our prospective study was designed in order to determine the sensitivity and specificity of thallium breast scanning as well as to delineate its potential role as a complement to mammography.

**METHODS**

**Patient Selection**

From September 1987 to June 1993, forty patients with breast abnormalities detected by mammography and/or physical examination were entered into our study from Boston City Hospital's surgical day clinic. The clinic is staffed by attending physicians and residents who rotate periodically. Given periodic staff turnover and divergent interests, the patient referral pattern proved erratic at best. We were, however, able to enroll enough patients for a preliminary assessment of the value of thallium scintigraphy in the diagnosis of breast cancer. The patient population in our study should be considered a random sample from the clinic.

Patients of Boston City Hospital with breast lesions detected by physical examination, mammography or both and scheduled for breast biopsy, fine needle aspirations or surgery were asked to participate. The study consisted of 38 women and 2 men, ages ranging from 31 to 77 yr. Four women had two lesions assessed in the study for a total of 44 breast lesions. Five patients were lost to follow-up because they failed to return for biopsy. There were a total number of 39 breast lesions used in the study. Thallium scintigraphy was performed before surgery, biopsy or aspiration.

Clinical presentation was as follows: twenty-one exclusive palpable masses, one palpable ulcerated mass with palpable axillary adenopathy, one palpable mass with skin erythema, one palpable mass with ecchymosis, eleven nonpalpable abnormalities, one exclusive breast discharge, one erythema and induration, one case of sole breast tenderness and one unknown. Mammographic findings yielded fourteen exclusive soft-tissue density masses; eight exclusive “malignant appearing calcifications”; one mass and “malignant appearing calcifications”; three breast asymmetries and “malignant appearing calcifications”; two mass and skin thickenings; one mass, “malignant appearing calcifications” and skin thickening; five exclusive dense breasts; one dense breast with skin thickening; one nipple inversion only; one unknown (mammography performed in Haiti); and two were postmastectomy and mammographies were not performed.

The data were considered in two groups of patients. Group A: patients (37 breast lesions were entered in the study, 32 completed the study) with no prior history of breast cancer. Group B: seven patients who had previous treatment of proven breast cancer and were suspected of having local recurrence due to palpable nodules at or near the surgical sites. Three patients diagnosed with breast cancer from Group A were also studied in Group B over the course of follow-up.

Informed consent was obtained from each patient. This prospective study was approved by the Institutional Review Board.

**Thallium Scintigraphy**

A single dose of 3 mCi of $^{201}$Tl-chloride was given intravenously. Scans were performed immediately after injection and at 3 hr postinjection. Each set of scans included both the anterior and lateral views of each breast using an Anger camera with a high-resolution collimator. A single 20% window, mercury x-ray set at 69–90 keV, was used. A preset count of 400,000 was used for the first view and the same exposure time was used for all subsequent views using the preset time format. If a patient was able to cooperate, the lateral view was taken in the prone position with the breast protruding through a hole cut through the table. The surface of the collimator was positioned in the vertical position parallel to and very close to the pendulous breast. This prone view enabled the breast to be imaged without compression or distortion by gravity, thus reducing background counts (Figs. 1, 2). SPECT was performed on only one patient who had a palpable parasternal mass in the postsurgical follow-up period (Group B). SPECT was used to separate uptake of the mass and the myocardium (Fig. 3).

**Interpretation**

Two physicians experienced in thallium scintigraphy independently reviewed and interpreted the scans without prior knowledge of biopsy or surgery results. Any disagreement regarding interpretation was discussed openly and resolved by consensus. Any focal or diffuse increased uptake of thallium in either breast, axilla or mediastinum was considered abnormal. Comparisons were made to the contralateral breast and axilla. The adjacent organs that are normally thallium-avid (heart, liver) were considered. After biopsy, the scintigraphic results were correlated with the pathological diagnosis and mammographic results.
Thallium was of the breast cancers. Surgery determined these abnormal foci to be malignant axillary lymph nodes. Two of the breast cancers were diagnosed with fine needle aspiration, while the remaining five were diagnosed by excisional biopsy. Tumor sizes ranged from 1.5 to 5.5 cm in the specimens. One of the breast lesions was non-palpable yet demonstrated a 0.5-cm spiculated mass on mammography. The remaining six lesions were palpable. On mammographic analysis, one lesion was not visible in the dense breasts of the patient, one had only microcalcifications, one had an inverted nipple with mass and two showed solely mass. Upon physical examination, one patient presented with an inflammatory carcinoma-like appearance with skin induration and erythema in addition to a palpable and radiographic mass. This patient exhibited thallium uptake in the skin of the breast as well as the breast mass on the delayed scan. However, in the entire series, delayed scans were not appreciably helpful in tumor detection as opposed to early scans. One mammogram was not available for review.

Thallium scans of 22 patients, including one male, were true-negatives, exhibiting no abnormal uptake of thallium in the breast in conjunction with benign biopsy results. On pathologic exam, the diagnosis included sclerosing adenosis, lipoma, focal fibrosis, apocrine metaplasia, gynecomastia, fibroadenoma, papillomatosis and fibrocystic change with focal adenosis. There were no benign adenomas. Ten of the 23 true-negatives had palpable masses. Five true-negative mammograms exhibited sole microcalcifications, nine had mass only, one had mass and microcalcification, three had dense breasts only, one had dense breast and skin thickening, one had asymmetry and microcalcifications, one had nipple inversion only and one (male) did not
have a mammography performed due to very small breast size.

There were two patients in Group A with false-negative thallium scans. Both had palpable and mammographic masses. One patient whose thallium scan was originally interpreted as negative demonstrated a 2-mm ductal carcinoma in situ on pathological examination. Her thallium scan was reviewed retrospectively, and, when compared to the contra-lateral side, slightly higher thallium uptake was visible.

There was one false-positive thallium scan. The patient presented with a nonpalpable, mammographically visible mass in one breast, although scan results indicated an increased bilateral thallium uptake relative to background soft tissue. Thallium uptake among the two breasts was greater in the breast containing the visible mass. The lesion on pathology was a hemangioma.

The overall sensitivity in this group was 80% and the specificity was 96%.

**Group B.** Seven patients who were treated for breast carcinoma with surgery and radiation therapy had thallium scans due to palpable nodules at treatment sites. Three of the patients were follow-ups from Group A who showed positive preoperative thallium scans. Five of the seven Group B patients had true-positive post-treatment thallium scans. Their biopsies indicated positive recurrence of carcinoma. The true-positives all had palpable masses. Two had mammographic masses and skin thickening (one of these also had microcalcifications), and the third patient had radiographically dense breast tissue. One patient had a true-negative thallium scan. She had a palpable mass and dense breasts on mammography. One patient had a false-negative thallium scan. This patient's biopsy indicated a microscopic focus of tumor recurrence. She had a nonpalpable mass with asymmetry and microcalcifications noted on mammography.

Since the number of patients in this group was small, no attempt was made to calculate the rate of sensitivity or specificity separately. A combination of data from Groups A and B (n = 39) yielded a sensitivity of 80% and specificity of 96% for thallium scintigraphy in the diagnosis of breast cancer.

**DISCUSSION**

In attempts to improve the diagnostic specificity of mammography, various radiotracers have been used in the past. Gallium, $^{99m}$Tc-pertechnetate and many bone-seeking agents, including $^{90}$Sr and $^{99m}$Tc-labeled phosphates, were reported to show high avidity in breast cancer. However, later investigations demonstrated that scintigraphy with these radiotracers was not clinically useful because of low specificity; these tracers were found to be avid in many benign lesions of the breast (28—35). Recently, PET with $^{18}$F-labeled deoxyglucose and tracers for estrogen receptors has been investigated for use in breast cancer detection. These results were extremely promising (36,38). Unfortunately, PET scanners are prohibitively expensive and are not yet widely available for general clinical use.

In 1987, we decided to investigate $^{201}$Tl as a potentially useful radiotracer for breast cancer based in part on past empirical reports. Thallium-201, in the form of the thallous cation, has been in use in medical scintigraphy since the early 1970s, mainly as a myocardial tracer. There are numerous reports of thallium avidity in tumors. These include hepatocellular carcinoma, lymphoma, gliomas of the brain, thyroid carcinoma, parathyroid adenoma, breast cancer and, recently, AIDS-related Kaposi's sarcoma (39—47). There have also been reports of incidental discovery of breast cancer in patients having stress thallium scans for evaluation of ischemic heart disease (39).

The exact mechanism of tumor cell uptake of thallium is incompletely known. The thallous ion is a monovalent cation with chemical properties similar to the potassium ion. Both the potassium and thallous ions share the same cell-membrane pathway, the "sodium-potassium ATPase pump." Cell culture experiments of both normal and neoplastic cells indicate that the high concentration of thallium in tumors is dependent on factors such as vascularity, cellularity and cell membrane alterations (48—52).

In 1985, Baker et al. reported that breast cancers showed higher concentrations of radioactive potassium compared to other benign lesions of the breast (53). Other Group I recommendations of the periodic table, chemical analogs of potassium such as rubidium and cesium, have also been reported to exhibit high concentrations in breast cancer. However, the overall sensitivity and specificity of the scintigraphs using these two radiotracers was not high enough for practical clinical use (34,35). Although not a Group I element, thallium possesses an ionic form that behaves as a biochemical analog of the potassium cation (K$^+$), most probably due to the similarity of their respective ionic radii (54). This supported our theory that thallium scintigraphy would be useful to differentiate between malignant and benign lesions of the breast. Thallium scintigraphy is clinically superior to potassium scintigraphy due to radioactive potassium's (K-42) emission of high energy photons. Because of its physical properties, including lower photon energy and a longer half-life, thallium has been used for myocardial imaging for the past 20 yr (54).

Mammography is well established as the most sensitive technique for detection of breast cancer, including nonpalpable cancers (carcinoma in situ, "minimal" cancer) (13,49). Thallium scintigraphy can be used to complement and improve the overall specificity of mammography in differentiating between benign and malignant lesions. In this respect, our results for thallium scintigraphy are very encouraging. In our study, only one of the benign lesions appeared thallium-avid. This high specificity makes thallium far superior to any other radiotracers used in the past. Both $^{99m}$Tc phosphates and pertechnetate were also taken up by some benign lesions of the breast, including breast adenomas. In this study, the diagnostic sensitivity and
specificity of thallium scintigraphy for initial diagnosis of breast carcinoma were 80% and 96% respectively.

The study resulted in only one false-positive thallium scan. This case raised disagreement in interpretation among the nuclear radiologists. The patient had bilateral focal persistent uptake of thallium at 3 hr, predominantly on the side of the palpable mass. After discussion, the scan was interpreted as positive without knowledge of the pathology results. Pathologic examination revealed a hemangioma. The slow flow through the abnormal vasculature in this benign tumor may have caused delayed retention of thallium locally.

Although the study yielded only one false-positive thallium scan, there were two cases of false-negative scans in presurgical breasts (Group A) and one false-negative in the treated group (Group B). The single false-negative in the treated group showed only a microscopic focus of carcinoma on pathologic examination, probably too small to concentrate enough thallium to be detectable. In retrospect, one of the two false-negatives in Group A could be considered positive due to its relatively low intensity of thallium uptake.

There are a number of scenarios in which the high specificity of thallium scintigraphy may be used as an adjunct to mammography and clinical examination. Among patients whose mammograms have demonstrated highly suspicious signs of malignancy (e.g., dominant mass, spiculated mass with or without microcalcifications), thallium scintigraphy would not be very useful to evaluate suspicious lesions because surgery or biopsy should be performed regardless of the scan results. However, thallium scintigraphy may potentially be very useful in evaluating the axilla for lymph node metastasis, the contralateral breast and baseline comparisons with future postoperative scans (Figs. 1 and 2). When patients' mammograms are abnormal yet considered indeterminate or benign, patient anxieties often oblige radiologists and surgeons to perform biopsies even on "probably benign" lesions with very low overall positive rates (24, 25). The conventional options are between biopsy and short-term periodic mammography (7, 10, 19–23, 27). This study suggests that a thallium scan may be offered as a third alternative. If the scan is positive, biopsy ought to be performed without delay. If negative, the probability of malignancy is even less and periodic short-term mammographic examination might be considered.

Dense breasts among younger patients are another difficult problem for mammography. Small tumors can be hidden by normal, dense glandular tissue (18, 55). Since normal glandular breast tissue is not thallium-avid, thallium scans can be used to evaluate these patients. For patients with breast cancer following mastectomy or radiation therapy, local recurrence is extremely difficult to distinguish from scar tissues both by clinical examination and mammography (18, 56, 57). A thallium scan would be very useful among these patients (Figs. 1C and 3B). Similar clinical applications using thallium scintigraphy have been established for the evaluation of recurrent brain gliomas and thyroid carcinoma (58, 59).

Delayed scanning was originally included in the protocol due to reports of improved specificity for evaluation of other tumors (39, 60). With the exception of one case, no significant difference in terms of tumor detection was found between the early and delayed scans in our patients.

In summary, thallium scintigraphy demonstrated high specificity for breast cancer. The technique warrants further study to determine whether the number of biopsy procedures can be reduced based on a combination of the scintigraphic and mammographic findings.

ACKNOWLEDGMENTS

The authors thank Hedwidge Brisson, Sheila Gavin, Merri Leemhuis and Mary Corrigan for technical assistance.

REFERENCES

2. Kelsey JL, Gammon MD. The epidemiology of breast cancer. CA 1991;41:
   146–165.
5. Sickles EA. Mammographic features of 300 consecutive non-palpable breast cancers. AJR 1986;146:661–663.
   51–65.
13. Sickles EA. Mammographic features of early breast cancer. AJR 1984;143:
   461–464.
   12–26.


