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

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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 mastectomies or lumpectomies. 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 breast 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 various radiotracers, including ^{99m}Tc-pertechnetate, ^{99m}Tc-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.

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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).

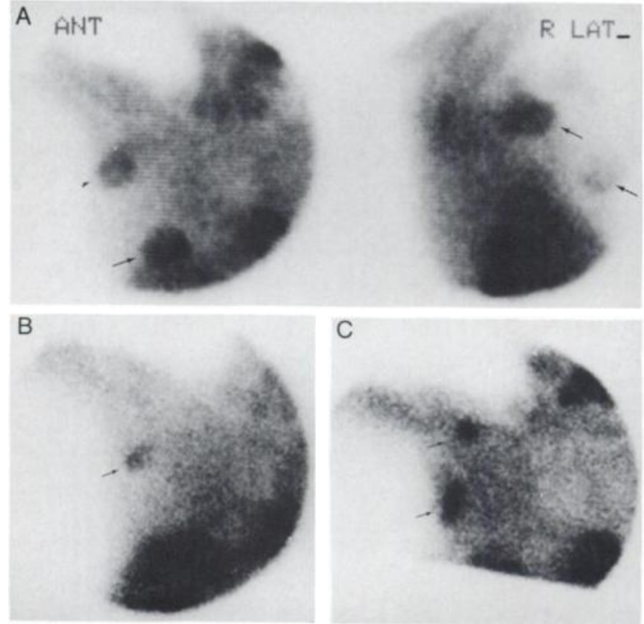

FIGURE 1. A 61-yr-old female who had a large palpable mass at her right breast. Mammogram demonstrated a 6-cm lobulated mass without calcification in her right breast. (A) Thallium scintigraphy detected large round areas of marked increased uptake at the right breast and axilla (arrows). The normal myocardium showed high uptake of thallium and should not be mistaken as abnormal uptake on the left side. (B) Follow-up thallium scintigraphy was performed after the patient received a course of preoperative chemotherapy (tomoxifen and adriamycin). The scan detected that uptake of the breast had returned to normal and that the abnormal axillary focus had markedly reduced in size. Surgery indicated poorly differentiated carcinoma with multiple axillary lymph node metastasis. (C) Ten months after mastectomy and node dissection, the patient and her physicians noticed multiple subcutaneous nodules adjacent to the surgical scars at her axilla and lateral chest wall. Repeat thallium scintigraphy determined these nodules to be thallium-avid (arrows). Biopsy of these nodules confirmed tumor recurrence.

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.

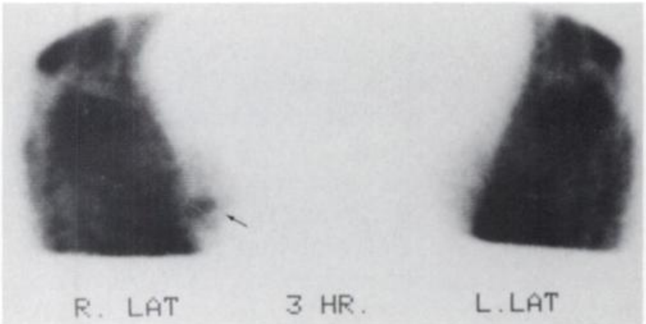

FIGURE 2. A 44-yr-old woman whose mother had had breast cancer. Her physician noted she had bilateral breast masses (3 cm in diameters). Mammograms showed that both breasts were relatively dense, and in the upper part (12 o'clock position) of her left breast there was a 2 × 2.5-cm mass. The posterior border of the mass was poorly demarcated. Although there was no definable mass indicated in the mammograms of the right breast, clusters of microcalcification were present in the same location as the palpable mass. Prebiopsy thallium scintigraphy demonstrated that uptake in the left breast was normal and that the right breast had marked and localized increased uptake of thallium (arrow). Biopsy was performed on both sides, revealing fibroadenoma on the left (true-negative) and carcinoma on the right breast (true-positive).

RESULTS

From September 1987 to June 1993, thallium scanning was performed on 44 breasts with abnormalities detected by mammography and/or physical examination. Five of these patients failed to return for biopsy and were lost to follow-up.

Group A. There were 32 breast lesions with available pathological results from biopsy or surgery. Two patients had bilateral breast biopsies (30 patients studied). Two of the 30 patients were male (age 36 and 70). The remaining 28 patients were female, ranging in age from 31 to 77 yr.

Seven patients, including one male in this group, had true-positive thallium scans that showed high focal uptake of thallium in abnormal breasts that proved to be malignant by pathologic examination (Figs. 1, 2). Two of these patients had abnormal foci of increased thallium uptake in the ipsolateral axillae of their abnormal breasts. 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 nonpalpable 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

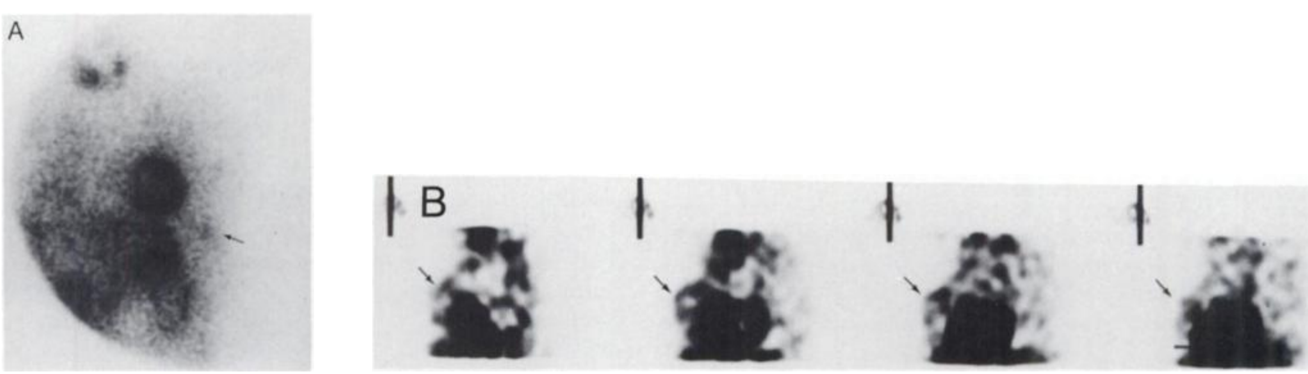

FIGURE 3. (A) A 33-yr-old female was noted to have a palpable mass in her left breast during routine physical examination. A mammography, performed in a foreign country, was reported to show a mass lesion in the left breast. Details of the radiographic findings were not available. Thallium scintigraphy before surgery detected a definite focus of increased uptake in her left breast clearly separate from the normal myocardium (arrow). Surgery determined the mass to be malignant carcinoma. (B) Two years after surgery, the patient developed a firm mass (3 × 4 cm) at the left parasternal chest wall. Repeat thallium scintigraphy was performed. In the planar image, increased uptake was present, but it was almost obscured by uptake in the myocardium (not shown). To confirm the finding, SPECT imaging was performed immediately after planar imaging. The sagittal section confirmed the abnormal uptake of the mass (arrows). The cold center of the mass was presumably due to central tumor necrosis. A biopsy of the mass confirmed recurrence of carcinoma.

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 1955, 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 cations 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 focally.

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

1. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the health insurance plan study: a randomized trial with breast cancer screening. *Natl Cancer Inst Mongr* 1985;67:65–74.
2. Kelsey JL, Gammon MD. The epidemiology of breast cancer. CA 1991;41: 146–165.
3. Moskowitz M, Gartside PS. Evidence of breast cancer mortality reduction: aggressive screening in women under age 30. *AJR* 1982;138:911–916.
4. Habbema JDF, van Oortmarssen GV, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screen: an analysis of the results of Health Insurance Plan of greater New York study. *JNCI* 1986;77:317–320.
5. Sickles EA. Mammographic features of 300 consecutive non-palpable breast cancers. *AJR* 1986;146:661–663.
6. Homer MJ. Nonpalpable breast abnormalities: a realistic view of the accuracy of mammography in detecting malignancies. *Radiology* 1984;153:831–832.
7. Stomper PC, Davis SP, Weidner N, Meyer JE. Clinically occult, noncalcified breast cancer: serial radiologic-pathologic correlation in 27 cases. *Radiology* 1988;169:621–626.
8. Bassett LW, Liu TH, Giuliano AE, Gold RH. The prevalence of carcinoma in palpable vs. impalpable, mammographically detected lesions. *AJR* 1991; 157:21–24.
9. Pollei SR, Mettler FA, Bartow SA, Moradian G, Moskowitz M. Occult breast cancer: prevalence and radiographic detectability. *Radiology* 1987; 163:459–462.
10. Rogers JV, Powell RW. Mammographic indications for biopsy of clinically normal breasts: correlation with pathologic findings in 72 cases. *AJR* 1972; 115:794–800.
11. Paredes ES. Ill-defined masses. In: *Atlas of film-screen mammography*. Baltimore, Munich: Urban and Schwartzenberg: 1989:139–189.
12. Sadoswsky N, Kopans DB. Breast Cancer. *Radiol Clin North Am* 1983;21: 51–65.
13. Sickles EA. Mammographic features of early breast cancer. *AJR* 1984;143: 461–464.
14. Moskowitz M. The predictive value of certain mammographic signs in screening for breast cancer. *Cancer* 1983;51:1007–1011.
15. Homer MJ. Nonpalpable mammographic abnormalities: timing the follow-up studies. *AJR* 1981;136:923–926.
16. Sickles EA. Breast calcifications: mammographic evaluation. *Radiology* 1986;160:289–293.
17. Mills RR, Davis R, Stacey AJ. The detection and significance of calcifications in the breast: radiologic and pathological study. *Br J Radiol* 1976;49: 12–26.
18. Kopans DB. *Breast imaging*. Philadelphia: Lippincott; 1989;34–135.
19. Hall FM, Storella JM, Selverstone DZ, Wyshak G. Nonpalpable breast lesions: recommendations for biopsy based on suspicion of carcinoma at mammography. *Radiology* 1988;167:353–368.
20. Hermann G, Janus C, Schwartz IS, Krivisky B, Bier S, Rabinowitz JG. Nonpalpable lesions: accuracy of pre-biopsy mammographic diagnosis. *Radiology* 1987;165:323–326.

21. Homer MJ. Imaging features and management of characteristically benign and probably benign lesions. *Radiol Clin North Am* 1987;25:939–951.
22. Stomper PC, Connolly JL, Meyer JE, Harris JR. Clinically occult ductal carcinoma in situ detected with mammography: analysis of 100 cases with radiologic-pathologic correlation. *Radiology* 1989;172:235–241.
23. Spivey GH, Perry BW, Clark VA, Coulson AH, Coulson WF. Predicting the risk of cancer at the time of breast biopsy: variation in the benign to malignant ratio. *Am Surgeons* 1982;48:326–332.
24. Meyer JE, Sonnenfeld MR, Greenes RA, Stomper PC. Preoperative localization of clinically occult breast lesions: experience at a referral hospital. *Radiology* 1988;169:627–628.
25. Brenner RJ, Sickles EA. Acceptability of periodic follow-up as an alternative to biopsy for mammographically detected lesions interpreted as probably benign. *Radiology* 1989;171:645–646.
26. Hall FM. Screening mammography—potential problems on the horizon. *N Engl J Med* 1986;314:53–55.
27. Kopans DB. "Early" breast cancer detection using techniques other than mammography. *AJR* 1984;143:465–468.
28. Cancroft ET, Goldsmith SJ. Tc-99m pertechnetate scintigraphy as an aid in the diagnosis of breast masses. *Radiology* 1973;106:441–444.
29. Villarreal RF, Parkey RW, Bonte FJ. Experimental pertechnetate mammography. *Radiology* 1974;111:657–661.
30. Richman SD, Ingle JN, Levenson SM, et al. Usefulness of gallium scintigraphy in primary and metastatic breast carcinoma. *J Nucl Med* 1975;16: 996–1001.
31. Richman SD, Brodey PA, Frankel RS, de Moss EV, Tormey DC, Johnston GS. Breast scintigraphy with Tc-99m-pertechnetate and Ga-67-citrate. *J Nucl Med* 1975;16:293–299.
32. McDougall IR, Pistenma DA. Concentration of Tc-99m diphosphonate in breast tissue. *Radiology* 1974;112:655–657.
33. Papavasiliou C, Angelakis P, Kostamis P, Constantinides C. Localization of Sr-87m in extraosseous tumors. *J Nucl Med* 1971;12:265–268.
34. Nishiyama H, Moskowitz M, Saenger EL, et al. Lack of specificity for detection of breast lesions with radioactive cesium chloride. *Surg Gyn Obstr* 1976;143:229–232.
35. Serafini AN, Raskin MM, Zand LC, Watson DD. Radionuclide breast scanning in carcinoma of the breast. *J Nucl Med* 1974;15:1149–1152.
36. Wahl RL, Cody R, Hutchins G, Mudgett E. Positron emission tomographic scanning of primary and the metastatic breast carcinoma with radio-labeled glucose analog 2-deoxy-F-18-fluoro-d-glucose. *N Engl J Med* 1991;324:200.
37. Mintun MA, Welch MJ, Siegel BA, et al. Breast cancer: PET imaging of estrogen receptors. *Radiology* 1988;169:45–48.
38. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991;32:623–648.
39. Lee VW, Fuller JD, O'Brien MJ, Parker DR, Cooley TP, Liebman HA. Pulmonary Kaposi sarcoma in patients with AIDS: scintigraphic diagnosis with thallium and gallium scanning. *Radiology* 1991;180:409–412.
40. Lee VW, Rosen MP, Baum A, et al. AIDS-related Kaposi sarcoma: findings on thallium scintigraphy. *AJR* 1988;151:1233–1235.
41. Hisada K, Tonami N, Migamae T, et al. Clinical evaluation of tumors with Tl-201 chloride. *Radiology* 1978;129:497–500.
42. Ochi H, Sawa H, Furuda T, et al. Tl-201 thyroid scintigraphy to evaluate benign and malignant lesions: usefulness of delayed scans. *Cancer* 1982;50: 236–240.
43. Hagenauer M, Silberstein EB. Detection of clinically occult axillary metastasis from breast cancer during stress Tl-201 scintigraphy. *Clin Nucl Med* 1991;16:520.
44. Senga O, Hanamura N, Terai N, et al. Clinical evaluation of Tl-201 chloride scintigraphy for breast tumors. *Kaku Igaku* 1985;22:1021–1028.
45. Waxman A, Ramanna L, Memsic L, Silberman A, Brenner J. Thallium scintigraphy in the differentiation of malignant from benign mass abnormalities of the breast [Abstract]. *J Nucl Med* 1990;31:767.
46. Sluyser M, Hoefnagel CA. Breast carcinomas detected by thallium-201 scintigraphy. *Cancer Lett* 1988;40:161–168.
47. Sehweil AM, McKillop JH, Milroy R, et al. Thallium-201 scintigraphy in the staging of lung cancer, breast cancer and lymphoma. *Nucl Med Commun* 1990;11:263–269.
48. Ando A, Ando I, Katayama. Biodistribution of Tl-201 in tumor bearing animals and inflammatory lesions. *Eur J Nucl Med* 1987;12:567–572.
49. Ito Y, Murankka A, Harada T, Matsudo A, Yokobayash T. Experimental study on tumor affinity of Tl-201. *Eur J Nucl Med* 1978;3:81–86.
50. Bakker-Grunwald T. Movement of the thallous ion across the ascites cell membrane. *J Membr Biol* 1979;47:171–183.
51. Dolts AM, Au PC. Thallous ion and the eye. *Invest Ophthalmol* 1971;10: 925–931.
52. Chauncey DM, Hagan PL, Halpern SE. Distribution of Cs-137, Tl-201, Hg-203, Pb-203, and Co-57 in rat hepatoma model in comparison with gallium. *Invest Radiology* 1978;13:40–45.
53. Baker WH, Nathanson IT, Selverstone B. Use of radioactive potassium (K42) in the study of benign and malignant breast tumors. *N Engl J Med* 1955;252:612–615.
54. Strauss WH, Pitt B. Thallium-201 as a myocardial imaging agent. *Semin Nucl Med* 1977;7:7–14.
55. Bassett LW, Gold RH. *Mammography, thermography and ultrasound in breast cancer detection*. New York, London: Grune and Stratton; 1982:13–52.
56. Paulus DD, Libshitz HI, Montague ED. Malignant masses in the therapeutically irradiated breasts. *AJR* 1980;135:789–795.
57. Peters ME, Fagerholm MI, Scalan KA, Voegeli DR, Kelcz F. Mammographic evaluation of the post-surgical and irradiated breast. *RadioGraphics* 1988;8:873–899.
58. Kaplan WD, Takvorian T, Morris JH. Thallium-201 brain tumor imaging: a comparative study with pathological correlation. *J Nucl Med* 1987;28:47–52.
59. Brendel AJ, Jeandot GR, Lefort G, Manciet G. Thallium-201 imaging in the follow-up of differentiated thyroid carcinoma. *J Nucl Med* 1988;29:1515–1520.
60. Lee VW. The importance of performing delayed thallium scintigraphy. *J Nucl Med* 1992;33:463–465.