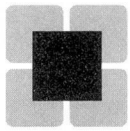

GARY S. HOFFMAN, MD, EDITOR

Bone scintigraphy screening in stage I–II breast cancer: Is it cost-effective?

KATHRYN A. WIKENHEISER, PHD, AND EDWARD B. SILBERSTEIN, MD

SUMMARY It is recommended that routine bone scans not be adopted for follow-up of patients with stage I–II breast cancer. Bone scintigraphy should be reserved for evaluation of patients presenting with symptoms suggestive of bone metastases.

KEY POINTS Bone scintigraphy as a screening modality for the detection of recurrent disease in patients with stage I–II breast cancer is not effective in prolonging patient survival or enhancing quality of life based on current scientific data. In addition, bone scintigraphic screening results in a significant cost to health care. Available data suggest that clinical follow-up is currently the best approach in detecting recurrent breast cancer. The data also show that 5-year survival is not prolonged in patients diagnosed by bone scan as part of an intensive follow-up scheme vs those followed by histories, physical examinations, and mammograms. Physician time spent in patient education may be a more cost-effective approach to patient follow-up than routine bone scans.

INDEX TERMS: RADIONUCLIDE IMAGING; BREAST NEOPLASMS; BONE NEOPLASMS; COST-BENEFIT ANALYSIS
CLEVE CLIN J MED 1996; 63:43–47

From the Department of Radiology and Medicine, the University of Cincinnati Hospital.
Address reprint requests to E.B.S., University of Cincinnati Medical Center, Mail Location 0577, P.O. Box 670577, Cincinnati, OH 45267-0577.

FOLLOW-UP PROCEDURES after successful primary treatment of stage I–II breast cancer are controversial[1–3] and vary among physicians.[4] Stage I breast cancer is defined as a tumor less than 2 cm in size (T1) without metastases to axillary nodes (N0). Stage II breast cancer is defined as a tumor less than 2 cm in size (T1) with metastases to axillary nodes (N1), or a tumor greater than 2 cm but less than 5 cm in size (T2) with (N1) or without (N0) metastases to axillary nodes. Many protocols for follow-up of stage I–II breast cancer patients consist of routine history and physical examinations along with diagnostic tests including blood counts, chemistry profiles, tumor marker studies, chest x-rays, mammograms, and bone scans. Signs and symptoms are the first indicators of recurrent breast cancer in 74% to 95% of cases, making history and physical examinations the best method for detecting recurrence.[4–6] Mammography is the one diagnostic test of clear benefit in follow-up of breast cancer since patients diagnosed with breast cancer have a threefold to fivefold higher risk of developing cancer in the

contralateral breast than developing the first cancer.[4,7] Tumor marker studies currently have no established role in surveillance of breast cancer patients.[5] The efficacy of the remaining diagnostic tests remains controversial.

The role of routine bone scans in the surveillance of stage I–II breast cancer patients is an issue of considerable debate, especially in the realm of cost-effective medicine. Due to the relatively high cost of bone scintigraphy and the high prevalence of early-stage breast cancer in the population, significant reductions in health care costs could be made by reducing or eliminating the number of bone scans done in asymptomatic patients. The goal of this paper is to reevaluate the role of routine bone scintigraphy in follow-up of asymptomatic stage I–II breast cancer patients. The evaluation is focused on three fundamental principles of cost-benefit analysis: (1) scientific data, (2) clinical impact, and (3) economics.

BONE SCINTIGRAPHY SCREENING FOR RECURRENT BREAST CANCER

Routine bone scans in successfully treated breast cancer patients are in effect screening tests since the patient population being tested is asymptomatic. Several criteria need to be fulfilled to make a screening test valuable: (1) the disease for which the test is designed must be a significant cause of mortality, (2) there must be a reasonably high prevalence of the disease in the screened population, (3) the screening method must be safe, (4) a preclinical phase of the disease must exist and be detected by the screening method with an acceptable sensitivity and specificity, and (5) therapy must be available so that survival or quality of life is significantly increased in early versus late diagnosis of the disease. Each of these issues will be addressed in the following discussion.

Breast cancer meets the first criterion for screening in that it is a significant cause of mortality. Breast cancer accounts for an estimated 46 000 deaths annually, and is second only to lung cancer as the leading cause of cancer deaths in women.[8] Mortality is higher in patients with recurrent breast cancer as compared to primary breast cancer patients because recurrence is more often associated with metastatic disease.

The incidence of stage I–II breast cancer is increasing in the United States due to the better methods available for detecting early-stage disease. From 1983–1990, 55% of diagnosed breast cancers were confined to the breast.[8] Recurrences occur in approximately 30% of early-stage breast cancer patients after primary treatment,[9–11] with the leading site of recurrence being the axial skeleton. In fact, 40% to 50% of all breast cancer patients develop their first recurrence in bone.[12] Thus, the high prevalence of early-stage breast cancer, along with the substantial risk of recurrences localized to bone, support the use of bone scintigraphy as a screening modality in follow-up of patients with early-stage breast cancer.

Bone scintigraphy is a safe procedure with a low morbidity. Radiopharmaceuticals, including technetium 99 MDP which is used in bone scintigraphy, are associated with minimal toxicity and a low incidence of adverse reactions. In a study involving 20 institutions, adverse reactions to radiopharmaceuticals occurred with an incidence of 1.1/100 000 doses per year.[13] Thus, radiopharmaceutical procedures, including bone scintigraphy, are remarkably safe and do not result in significant morbidity or mortality.

Bone scintigraphy is currently accepted by most physicians as the most sensitive technique available to detect bone metastases in cancer patients. Crippa et al[14] reported a sensitivity of 98% in follow-up of patients with early-stage breast cancer. However, since bone scan abnormalities can represent benign disease, diagnostic dilemmas arise when abnormalities are detected in asymptomatic patients without known metastatic disease. The overall false-positive rate of bone scans ranges from 10% to 22%,[2,14,15] and the false-negative rate is estimated at 10%.[15] Using Bayes' theorem, the positive predictive value of bone scans in patients with stage I–II breast cancer was calculated as 11.9%.[16] This would indicate that approximately one in nine patients with abnormal bone scans would have bone metastases. Interestingly, Crippa et al[14] reported a positive predictive value of 73% when performing routine bone scans in early-stage breast cancer patients. The differences in estimates of positive predictive values and specificity may be influenced by the definition of "positive" tests. Benign diseases often result in predictable patterns on bone scans and can be differentiated from malignant disease. However, if both benign and malignant changes on bone scans are designated as positive scans, specificity and positive predictive values are significantly altered. Another explanation is that differences in pretest prevalence of disease may exist between studies. This emphasizes the point that study results must be carefully interpreted.

Bone scintigraphy is capable of detecting preclinical metastases in patients with early-stage breast cancer. However, signs and symptoms are a more common indicator of bone metastases than abnormalities on routine bone scans. In a study by Pandya et al,[6] 65% of patients with osseous involvement were first identified through signs and symptoms of metastatic disease, whereas only 18% were recognized by routine bone scintigraphy. Derimanow et al[17] noted that the chances of discovering a metastatic lesion with bone scintigraphy was increased fivefold if the patient was symptomatic or there was clinical suspicion of metastatic disease based on abnormal laboratory values. In addition, Burkett et al[18] demonstrated that true positive results of bone scans were improved if the screened population was symptomatic vs asymptomatic. In evaluating the efficacy of routine bone scans in asymptomatic patients, Wickerham et al[19] found that at most, 0.6% of the total number of screening bone scans detected bone metastases when routine bone scans were performed at 6-month intervals for 3 years and yearly thereafter. Thus, although the sensitivity of bone scans is high in detecting bone metastases, many scans are required to diagnose a small percentage of asymptomatic patients with recurrent disease. Furthermore, the specificity of bone scintigraphy is variable based on the interpreter's ability to differentiate benign from malignant disease. It is important to emphasize however, that the specificity and sensitivity of bone scintigraphy is improved when the pretest suspicion of disease is higher due to patient symptomatology.

The final screening test criterion to address is whether survival or quality of life is significantly increased in early vs late diagnosis of breast cancer recurrence. The presumption that early diagnosis and treatment of recurrent breast cancer leads to prolonged survival and better psychosocial functioning is the reason given most often for intensive follow-up. To test this presumption, Rosselli Del Turco et al[10] recently conducted a prospective, randomized trial to evaluate the effectiveness of early detection of intrathoracic and bone metastases in reducing mortality in early-stage breast cancer patients. Patients were randomized into an "intensive" or "control" follow-up protocol. The intensive follow-up protocol included chest x-rays and bone scans at 6-month intervals for a 5-year follow-up period. The frequencies of history and physical examinations and mammograms were identical in the two groups. The results showed no differences in 5-year mortality between the two follow-up groups despite earlier diagnosis of recurrence in the intensive protocol group. A similar study was conducted by the Interdisciplinary Group for Cancer Care Evaluation (GIVIO),[11] wherein the intensive protocol included annual bone scans and liver echograms, semiannual chest x-rays, and frequent blood levels of alkaline phosphatase and gamma glutamyltranspeptidase for a 6-year follow-up period. The GIVIO study reported no difference in mean time to detection of distant metastases between the intensive and control follow-up groups. Additionally, no difference in survival was noted between the two groups.

Quality-of-life issues were assessed in the GIVIO study using self-administered questionnaires. No differences between the two follow-up groups were detected in the areas of quality-of-life perception, overall health perception, body image, emotional well being, social functioning, or symptomatology. When asked, 70% of the patients wanted to be seen frequently by a physician and undergo diagnostic tests even if free of symptoms. Despite this, no difference in satisfaction with care was detected between the intensive and control follow-up groups. Therefore, the studies conclude that follow-up based on routine execution of a battery of diagnostic tests, including bone scans, is not superior to clinical follow-up of patients with early-stage breast cancer.

COST ANALYSIS

The 1995 estimated incidence of breast cancer in females is 182 000. Cancer limited to the breast accounts for 55% of all breast cancer, or 100 100 cases. Assuming yearly bone scans for a 5-year follow-up period (the time period when the majority of recurrences occur[3,14]), a cost of $246 246 000 would accrue, assuming a 30% recurrence rate over 5 years (6% per year). This cost estimate is based on a total body bone scan cost of $600. Follow-up studies done to work up false-positive tests would add an additional cost. The cost for work-up of false-positive tests is difficult to predict, but would likely be substantial since 41 041 cases of false-positive results would be expected annually based on a 10% false-positive rate.

Another way to view the cost of bone scintigraphy as a screening modality is to estimate the cost required to diagnose a case of recurrent disease. In a

study by Thomsen et al,[20] 234 bone scans were required to discover one case of bone metastases when bone scans were performed semiannually for the first year and yearly thereafter. Based on this study, the cost for detecting one case of recurrent disease would be $140 400. Therefore, the use of bone scintigraphy as a screening modality for recurrent disease in patients with early-stage breast cancer represents a substantial cost to health care.

CONCLUSIONS

The role of bone scintigraphy in preoperative staging and follow-up of patients with stage I–II breast cancer is currently being debated. Preoperative staging bone scans, after histological diagnosis of breast cancer, are often obtained in asymptomatic patients despite data arguing against this approach. Studies by Kunkler et al[21] and Butzelaar et al[22] concluded that there is no justification for using routine bone scintigraphy as a screening test for metastases in newly diagnosed asymptomatic patients with early clinical stages of breast cancer. In these studies, skeletal scintigraphy abnormalities were detected in only 3% to 7% of patients with stage I–II breast cancer. In addition, the abnormal bone scan results could not be proven to represent metastases, and the false-positive rate was as high as 13.6%. Bone scintigraphy in patients prior to histological confirmation of breast cancer would be of even lower yield since the positive predictive value (number of cancers detected/number of biopsies recommended) is 13% to 34% for palpable and nonpalpable, mammographically detected lesions.[23,24] Based on these data, routine preoperative bone scintigraphy in asymptomatic patients prior to histological diagnosis of breast cancer is not recommended. In addition, preoperative bone scintigraphy after histological evidence of breast cancer is obtained is of low yield in asymptomatic patients, and therefore is unlikely to alter patient management with stage I–II breast cancer.

Bone scintigraphy as a screening modality for the detection of recurrent disease in patients with stage I–II breast cancer is not effective in prolonging patient survival or enhancing quality of life based on current scientific data. In addition, bone scintigraphic screening results in a significant cost to health care. It is recommended that routine bone scans not be adopted for follow-up of patients with stage I–II breast cancer. Bone scintigraphy should be reserved for evaluation of patients presenting with symptoms suggestive of bone metastases.

Clinical patient follow-up without routine diagnostic testing is often referred to as a minimalistic approach. Wertheimer[3] argued against a minimalistic approach in the follow-up of patients with early-stage breast cancer. He stated that lack of definite survival advantages does not justify a "nihilistic" approach to early detection of metastases. He also quoted a fundamental principle of tumor biology, namely that "systemic therapy should be administered as early as possible in the life span of a tumor to avoid drug-resistant cells and theoretically to increase the possibility of cure...when the number of cells is smallest," to support his stance. His statements assume that clinical follow-up is a "nihilistic" approach and that therapy for treatment of recurrent breast cancer is effective. Available data suggest that clinical follow-up is currently the best approach in detecting recurrent breast cancer. The data also show that 5-year survival is not prolonged in patients diagnosed by bone scan as part of an intensive follow-up scheme vs those followed by histories, physical examinations, and mammograms. Although additional research will hopefully change this in the future, it is recommended that clinical practices be based on currently available scientific data. Thus, a minimalistic approach to follow-up of patients with breast cancer is appropriate. However, it is very important to point out that the approach to patient follow-up must be continually modified as research results in better diagnostic tests and more effective therapy.

Intensive follow-up protocols are sometimes favored over minimalistic approaches based on the assumption that patients would reject the concept of minimalism. In the GIVIO study, patients did prefer diagnostic testing even if asymptomatic. However, they reported no differences in satisfaction of care when placed in intensive vs minimalistic follow-up protocols. These results suggest that patients do not equate fewer diagnostic tests with suboptimal care. Although further studies are needed to adequately address this issue, it is recommended that physicians spend adequate time with patients explaining the benefits and inadequacies of diagnostic tests. Patients frequently hold misconceptions concerning their disease and its treatment which are unrecognized by physicians.[25] In addition, only 39% of patients receive "thorough" information on their disease.[26] At an estimated cost of $100

per 40-minute office visit, physicians could spend 4 hours with a patient for the cost of one bone scan. Thus, physician time spent in patient education may be a more cost-effective approach to patient follow-up than routine bone scans.

REFERENCES

1. **Schapira DV.** Breast cancer surveillance—a cost effective strategy. Breast Cancer Res Treat 1993; **25:**107–111.
2. **Schapira DV.** A minimalist policy for breast cancer surveillance. JAMA 1991; **265:**380–382.
3. **Wertheimer MD.** Against minimalism in breast cancer follow-up. JAMA; **265:**396–397.
4. **Loomer L, Brockschmidt JK, Muss HB, Saylor G.** Postoperative follow-up of patients with early breast cancer. Cancer 1991; **67:**55–60.
5. **Loprinzi CL.** It is now the age to define the appropriate follow-up of primary breast cancer patients. J Clin Oncol 1994; **12:**881–883.
6. **Pandya KJ, McFadden ET, Kalish LA, Tormey DC, Taylor SG, Falkson G.** A retrospective study of earliest indicators of recurrence in patients on eastern cooperative oncology group adjuvant chemotherapy trials for breast cancer. Cancer 1985; **55:**202–205.
7. **Mellink WAM, Holland R, Hendricks JHCL, Peeters PHM, Rutgers EJT, van Daal WAJ.** The contribution of routine follow-up mammography to an early detection of asynchronous contralateral breast cancer. Cancer 1991; **67:**1844–1848.
8. **Wingo PA, Tong T, Bolden S.** Cancer statistics, 1995. CA Cancer J Clin 1995; **45:**8–30.
9. **Hannisdal E, Gundersen S, Kvaloy S, et al.** Follow-up of breast cancer patients stage I–II: a baseline strategy. Eur J Cancer 1993; **29A:**992–997.
10. **Rosselli Del Turco M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V.** Intensive diagnostic follow-up after treatment of primary breast cancer. JAMA 1994; **271:**1593–1597.
11. **GIVIO Investigators.** Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. JAMA 1994; **271:**1587–1592.
12. **McNeil BJ, Polak JF.** An update on the rationale for the use of bone scans in selected metastatic and primary bone tumors. In: Pauwels EKJ, Schutte, HE, Taconis WK, editors. Bone scintigraphy. Martinus Nijhoff Publishers. 1981:187–207.
13. **Silberstein E.** Incidence of adverse reactions to radiopharmaceuticals. J Nucl Med 1992; **33:**1025. Abstract.
14. **Crippa R, Seregni E, Agresti R, Bombardieri E, Buraggi GL.** Bone scintigraphy in breast cancer: a ten-year follow-up study. J Nucl Biol Med 1993; **37:**57–61.
15. **Kennedy H, Kennedy N, Barclay M, Horobin M.** Cost efficiency of bone scans in breast cancer. Clin Oncol 1991; **3:**73–77.
16. **Khanderkar JD, Burkett FE, Scanlon EF.** Sensitivity, specificity and predictive value of bone scans in breast cancer. Proc Soc Clin Oncol 1978; **19:**379. Abstract.
17. **Derimanov SG.** "For" or "against" bone scintigraphy of patients with breast cancer. Nucl Med Comm 1987; **8:**79–86.
18. **Burkett FE, Scanlon EF, Garces RM, Khandekar JD.** The value of bone scan in the management of patients with carcinoma of the breast. Surg Gyn Obst 1979; **149:**523–525.
19. **Wickerham L, Fisher B, Cronin W.** The efficacy of bone scanning in the follow-up of patients with operable breast cancer. Breast Cancer Res Treat 1984; **4:**303–307.
20. **Thomsen HS, Rasmussen D, Munch O, et al.** Bone metastases in primary operable breast cancer: the role of a yearly scintigraphy. Eur J Cancer Clin Oncol 1987; **23:**779–781.
21. **Kunkler IH, Merrick MV, Rodger A.** Bone scintigraphy in breast cancer: a nine year follow-up. Clin Radiol 1985; **36:**279–282.
22. **Butzelaar RMJM, van Dongen JA, van der Schoot JB, van Ulden BJG.** Evaluation of routine pre-operative bone scintigraphy in patients with breast cancer. Eur J Cancer 1977; **13:**19–21.
23. **Bassett LW, Liu TH, Giuliano AE, Gold RH.** The prevalence of carcinoma in palpable vs impalpable, mammographically detected lesions. Am J Roentgen 1991; **157:**21–24.
24. **Malloy M, Azarow K, Garcia VF, Daniel JR.** Enhanced detection of preinvasive breast cancer: combined role of mammography and needle localization biopsy. J Surg Oncol 1989; **40:**152–154.
25. **Mackillop WJ, Stewart WE, Ginsburg AD, Stewart SS.** Cancer patients' perceptions of their disease and its treatment. Br J Cancer 1988; **58:**355–358.
26. **GIVIO.** What doctors tell patients with breast cancer about diagnosis and treatment: findings from a study in general hospitals. Br J Cancer 1986; **54:**319–326.