8. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid.* 2003;13: 45–56.
9. Spencer CA. Challenges of serum thyroglobulin (Tg) measurement in the presence of Tg autoantibodies. *J Clin Endocrinol Metab.* 2004;89:3702–3704.

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Diffuse Tracer Uptake in Scintimammography: Not as Nonspecific or Benign as Originally Believed?

TO THE EDITOR: We read with interest the recent article by Dr. Mathieu et al. (*1*) regarding the role of scintimammography in initial breast cancer diagnosis, detection of recurrence, and evaluation of tumor extent when the results from a protocol encompassing mammography, ultrasound, and fine-needle aspiration biopsy are inconclusive. Prompted by the results and discussion arising from this work, we feel the need to underline the significance of the interpretation of a diffuse radiotracer uptake pattern that is often observed in many scintimammography studies. According to the authors (*1*), faint, diffuse radiopharmaceutical uptake was shown to correspond to lobular or in situ breast carcinoma and therefore should not be systematically classified as nonspecific or benign.

We certainly agree with this observation and the notion that any diffuse uptake pattern in scintimammography should not be considered as a nonspecific or false-positive finding but should draw attention and be further investigated. In a previous series of ours (*2*), we enrolled patients with suggestive breast lesions (on physical examination or mammography) that were scintimammographically evaluated (planar imaging) with ^{99m}Tc-sestamibi or ^{99m}Tc-labeled dimercaptosuccinic acid [^{99m}Tc-(V)DMSA]. The occurrence of a diffuse, widespread pattern of radiotracer uptake was consistently associated with the presence of histologically confirmed preinvasive breast lesions. In particular, a locally diffuse, heterogeneous (patchy), poorly circumscribed increased uptake—predominantly with ^{99m}Tc-(V)DMSA and to a lesser degree but more specifically with ^{99m}Tc-sestamibi—was associated with in situ carcinoma, both ductal and lobular. This uptake was independent of the presence of suggestive microcalcifications on mammography, because it occurred in several lesions mammographically classified as class 3 or even class 2 in some cases, according to the Breast Imaging Reporting and Data System (*3*). A similar diffuse uptake pattern, although not patchy but more homogeneous, was observed in some benign but highly proliferative and potentially premalignant cases of usual-type or atypical-type breast hyperplasia, but never in the benign lesions of fibrosis, adenosis, or ductal dilatation (*2*).

Furthermore, the intensity of diffuse ^{99m}Tc-(V)DMSA uptake in both ductal and lobular carcinoma in situ and hyperplastic breast lesions was found to be related to their proliferative activity, as immunohistologically demonstrated by Ki-67 expression (*2*); that is, preinvasive—in situ or hyperplastic—breast lesions at high risk of evolving to invasive malignancy are associated with this particular ^{99m}Tc-(V)DMSA uptake pattern. This finding is in accordance with in vivo (*4*) and in vitro (*5*) reports that associate ^{99m}Tc-(V)DMSA uptake with cellular proliferation activity in invasive breast cancer. With regard to ^{99m}Tc-sestamibi, although it appears to be less sensitive in displaying this diffuse distribution in ductal or lobular carcinoma in situ (probably because its cellular uptake is not stringently associated with proliferative activity (*4,6,7*), it maintains a higher specificity than ^{99m}Tc-(V)DMSA in imaging in situ carcinoma, because its degree and intensity of uptake by nonmalignant breast hyperplasia are considerably lower (*2*).

It might therefore be useful if the reading of both planar and tomographic (SPECT) scintimammography studies incorporated not only the typically pathologic sites of focal tracer accumulation but also regions of diffuse uptake suggestive of preinvasive abnormalities. A scoring system for scintimammography that would classify the scintigraphic findings in proportion to their likelihood for malignancy in mammography, in a way similar to that in which the Breast Imaging Reporting and Data System classifies mammographic findings (*3*), might prove useful in increasing the diagnostic accuracy of scintimammography to detect invasive and preinvasive breast carcinoma, both at initial presentation and at suspected relapse after treatment. In such a diagnostic approach, any focally increased radiotracer uptake (with or without a coexistent diffuse uptake pattern) could be characterized as highly suggestive of invasive malignancy, with or without a preinvasive component (class 4); a diffuse inhomogeneous radiotracer distribution could be characterized as suggestive of a preinvasive lesion (class 3); a diffuse homogeneous uptake could be characterized as probably benign (epithelial hyperplasia) (class 2); and a study without any increased uptake could be characterized as negative (class 1). Hence, a class 3 patient, despite lacking the typical diagnostic criterion of focally increased uptake corresponding to invasive cancer, may be subject to a closer follow-up and possibly a breast biopsy, because it might reveal an underlying in situ or diffuse lobular breast carcinoma.

Conclusively, because scintimammography is an important complement to mammography in patients with suspected breast cancer (*1*) and may also reveal suggestive findings even in mammographically nonsuggestive cases (*2*), we propound that such a scoring system for scintimammography studies deserves to be prospectively evaluated with regard to its reliability in establishing an early and accurate diagnosis as well as in influencing patient management and therapeutic decision making.

REFERENCES

1. Mathieu I, Mazy S, Willemart B, Destine M, Mazy G, Lonneux M. Inconclusive triple diagnosis in breast cancer imaging: is there a place for scintimammography? *J Nucl Med.* 2005;46:1574–1581.
2. Papantoniou V, Tsiouris S, Mainta E, et al. Imaging in situ breast carcinoma (with or without an invasive component) with technetium-99m pentavalent dimercaptosuccinic acid and technetium-99m 2-methoxy isobutyl isonitrile scintimammography. *Breast Cancer Res.* 2005;7:R33–R45.
3. *Breast Imaging Reporting and Data System (BI-RADS).* 2nd ed. Reston, VA: American College of Radiology; 1995.
4. Papantoniou VJ, Souvatzoglou MA, Valotassiou VJ, et al. Relationship of cell proliferation (Ki-67) to ^{99m}Tc-(V)DMSA uptake in breast cancer. *Breast Cancer Res.* 2004;6:R56–R62.
5. Denoyer D, Perek N, Le Jeune N, Cornillon J, Dubois F. Correlation between ^{99m}Tc-(V)-DMSA uptake and constitutive level of phosphorylated focal adhesion

kinase in an in vitro model of cancer cell lines. *Eur J Nucl Med Mol Imaging.* 2005;32:820–827.
6. Cutrone JA, Yospur LS, Khalkhali I, Tolmos J, Devito A, Diggles L. Immunohistologic assessment of technetium-99m-MIBI uptake in benign and malignant breast lesions. *J Nucl Med.* 1998;39:449–453.
7. Cwikla JB, Buscombe JR, Kolasinska AD, Parbhoo SP, Thakrar DS, Hilson AJ. Correlation between uptake of Tc-99m sesta-MIBI and prognostic factors of breast cancer. *Anticancer Res.* 1999;19:2299–2304.

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REPLY: My coauthors and I read with interest the letter from Dr. Papantoniou et al. Much of the letter reports on the use of ^{99m}Tc-(V)DMSA for imaging of breast lesions. We did not use this tracer in our study and have only little experience with it. The authors agree with us that a faint and diffuse sestamibi uptake must not be considered as nonspecific or probably benign. The idea of a scoring system for scintimammography is interesting and must be validated. In our study, invasive—not only in situ—lobular carcinoma was associated with a faintly diffuse and heterogeneous uptake of sestamibi. Therefore, we think that the proposed class 3 should not refer only to a preinvasive component. Differentiating in situ from invasive components within a heterogeneous area of tracer uptake is probably not possible because of the limited spatial resolution of SPECT. After initial validation, such a scoring system could be tested in a prospective, preferably multicentric, clinical setting. A robust scoring system would certainly increase the strength of scintimammography as a second-line breast imaging technique.

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Use of ^{99m}Tc-Sestamibi Scintigraphy in Multiple Myeloma

TO THE EDITOR: We read with great interest the excellent review on imaging of malignant bone involvement by Einat Even-Sapir published in the August issue of *The Journal of Nuclear Medicine* (*1*). We would like to comment on the use of ^{99m}Tc-sestamibi in multiple myeloma. In recent years, different groups have reported a high accuracy for this tracer in the detection of active disease (*2–7*). In particular, ^{99m}Tc-sestamibi scintigraphy has shown a positive predictive value of 100% and a negative predictive value of 83% in the diagnosis of active multiple myeloma and a positive predictive value of 84% and a negative predictive value of 100% in identifying advanced stages (i.e., II or III) of disease (*2*). Positive ^{99m}Tc-sestamibi whole-body results were found in 30% of patients with no evidence of multiple myeloma on a radiologic full skeletal survey, and in the majority (76%), the scintigraphic findings agreed with the subsequent clinical follow-up (*3*). Moreover, there are consistent published data on the use of ^{99m}Tc-sestamibi in follow-up of patients with multiple myeloma (*4–6*). In particular, all patients with a negative ^{99m}Tc-sestamibi result at follow-up were actually in disease remission (either complete or partial), whereas 86% of those with a positive ^{99m}Tc-sestamibi result had disease progression (*4*). Even-Sapir expressed his concern about using ^{99m}Tc-sestamibi in follow-up studies because of the development of multidrug resistance, which may block tracer accumulation (*1*). In our experience, the multidrug-resistant phenotype is characterized by a faster washout of ^{99m}Tc-sestamibi rather than a lower early tracer uptake (*8,9*), and washout rates of ^{99m}Tc-sestamibi were indeed predictive of response to chemotherapy in these patients (10). Therefore, when images are acquired 10 min after tracer injection, the diagnostic accuracy of ^{99m}Tc-sestamibi scanning is not significantly affected by P-glycoprotein overexpression, and patients with multiple myeloma can confidently be monitored with ^{99m}Tc-sestamibi scanning after treatment.

REFERENCES

1. Even-Sapir E. Imaging of malignant bone involvement by morphologic, scintigraphic, and hybrid modalities. *J Nucl Med.* 2005;46:1356–1367.
2. Pace L, Catalano L, Pinto AM, et al. Different patterns of technetium-99m sestamibi uptake in multiple myeloma. *Eur J Nucl Med.* 1998;25:714–720.
3. Catalano L, Pace L, Califano C, et al. Detection of focal myeloma lesions by technetium-99m-sestaMIBI scintigraphy. *Haematologica.* 1999;84:119–124.
4. Pace L, Catalano L, Del Vecchio S, et al. Predictive value of technetium-99m sestamibi in patients with multiple myeloma and potential role in the follow-up. *Eur J Nucl Med.* 2001;28:304–312.
5. Balleari E, Villa G, Garre S, et al. Technetium-99m-sestamibi scintigraphy in multiple myeloma and related gammopathies: a useful tool for the identification and follow-up of myeloma bone disease. *Haematologica.* 2001;86:78–84.
6. Svaldi M, Tappa C, Gebert U, et al. Technetium-99m-sestamibi scintigraphy: an alternative approach for diagnosis and follow-up of active myeloma lesions after high-dose chemotherapy and autologous stem cell transplantation. *Ann Hematol.* 2001;80:393–397.
7. Alexandrakis MG, Kyriakou DS, Passam F, Koukouraki S, Karkavitsas N. Value of Tc-99m sestamibi scintigraphy in the detection of bone lesions in multiple myeloma: comparison with Tc-99m-ethylene diphosphonate. *Ann Hematol.* 2001; 80:349–353.
8. Fonti R, Del Vecchio S, Zannetti A, et al. Functional imaging of multidrug resistant phenotype by ^{99m}Tc-MIBI scan in patients with multiple myeloma. *Cancer Biother Radiopharm.* 2004;19:165–170.
9. Pace L, Catalano L, Del Vecchio S, et al. Washout of ^{99m}Tc-sestamibi in predicting response to chemotherapy in patients with multiple myeloma. *Q J Nucl Med.* 2005;49:281–285.

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