Sestamibi Scanning of Breast Cancer

TO THE EDITOR: Khalkhali et al. (*1*) are to be commended for their development of sestamibi as an agent for the evaluation of potential breast cancer. However, as a practitioner of both breast imaging and nuclear medicine, I wish to comment on the difficulties of using this method in clinical practice.

To understand the clinical problems that sestamibi breast scanning can present, let us consider first the group of patients that Khalkhali et al. (*1*) recently reported—patients with mammographic or clinical masses. Then let us consider a group that the authors did not include in this article but have referred to previously (*2*)—patients with mammographically dense breasts who are difficult to examine.

Patients with mammographic or palpable masses are the patients who are currently referred for biopsy. The only reason to study these patients with sestamibi scanning would be to exclude some from biopsy.

Is it important to avoid biopsy? Breast biopsy is not nearly as difficult a procedure as it was several years ago. Our practice has changed almost entirely to vacuum-assisted 11-gauge core needle biopsies, and we find that these are very minor surgical procedures. The most discomfort that the patients have is neck and extremity pain from lying still for 30 min. They are left with a 5-mm skin nick that is covered with a single Steri-Strip (3M Health Care, St. Paul, MN). The procedure has a low complication rate, and the false-negative rate is reported to average 2.8% (range, 0.3%–8.2%) (*3*), which is substantially the same as the 2.0% miss rate (range, 0%–8%) for needle localization and open biopsy (*3*). (Technical note: These false-negative rates were taken from studies using 14-gauge Biopty guns [Bend Urological, Covington, GA]. The current state-of-the-art system is an 11-gauge vacuum-assisted device that obtains about 9 times as much tissue per pass as the Biopty gun. No data on the false-negative rate for the vacuum-assisted device have yet appeared. However, it is likely that the false-negative rate will be lower and certainly no more than the rate for the 14-gauge device.) Any modality that would divert a woman from having a biopsy needs to have a false-negative rate near zero, because obtaining the definitive, histologic answer is now so easy.

We should also consider what would happen to those women diverted from a biopsy. For a hypothetical group of 100,000 patients who have been referred for screening, approximately 250 will harbor cancer (*4*). Using the 75.4% sensitivity found by Khalkhali et al. (*1*) (24.6% false-negative rate), the scan results of approximately 61 patients will be negative. If sestamibi is being used to determine who does not undergo biopsy, then these patients will not undergo biopsy and their cancer will be missed. This outcome is not acceptable in current practice, because these patients were destined to have a biopsy and their cancer would have been discovered except for the result of the sestamibi scan. The problem is even greater when one considers that the sestamibi scan will preferentially miss small tumors, approximating 50% of cancer cases (*1*). These are the most curable cases. The ability of mammography to find nonpalpable tumors is the reason that it has increased breast cancer survival, and the effect on survival is the reason we cannot afford to miss nonpalpable tumors.

It is apparent that in the interest of avoiding a quick, comfortable, safe, definitive, and relatively inexpensive invasive procedure, we will be missing 25% of the cancer cases that we would otherwise find, with a disproportionate number being low-stage lesions. I cannot recommend this approach to my referring physicians or my patients.

Concerning the second group, those patients with mammographically dense breasts, Khalkhali et al. (*1*) appropriately observe that it contributes disproportionately to the false-negative rate of mammography, which they note as 5%–15%. We are all attempting to reduce this false-negative rate, but I do not believe that sestamibi will help. Consider, again, the hypothetical group of 100,000 women of whom approximately 250 have cancer. If we assume a mammographic false-negative rate of 10%, then we will miss 25 women with cancer. To find these women, we will have to screen the entire mammographically negative population (99,750 + 25, or 99,775). Because the specificity of sestamibi in the report of Khalkhali et al. was 82.7%, this population will have 82,514 women with negative mammography results and 17,261 with positive results. We would then have to perform a biopsy on 17,261 women to find 25 additional cases of cancer (1 positive biopsy result in 690 patients).

If we are to perform a biopsy on lesions that are mammographically negative and sestamibi positive, we face the substantial problem of localizing the lesion for surgery. In most cases, the best we can do with sestamibi is to localize the lesion to 1 quadrant. In the worst case, the lesion may be found deep in the central part of the breast. The surgeon (and the patient) are then left rather victimized, with a report that says there may be cancer in the breast but the sestamibi scan can give only an approximate location. In this circumstance, the surgeon may have to take out a quadrant or more without really knowing if the lesion was obtained. If the pathology findings are negative, the surgeon does not know whether to assume that the sestamibi scan was false-positive or to try another excision. The surgeon will always be left wondering, "Did I get it or not?" and there really is no way of knowing. For these reasons, I maintain that we might be doing more harm than good in this clinical situation.

In summary, if we were to use sestamibi breast imaging in patients who have positive mammographic or sonographic findings and are thus referred for biopsy, we would risk missing many curable cases of cancer in the interest of avoiding a trivial invasive procedure. On the other hand, if, in the interest of reducing the false-negative results inherent in mammography and sonography, we were to use sestamibi breast imaging in patients who have negative findings from a conventional imaging work-up, we would have to perform a biopsy on 690 women to find 1 case of cancer. We would also face the substantial tumor-localization problem, which is certain to disillusion our referring surgeons.

MRI needs to be mentioned in this discussion. Its mechanism is similar to that of sestamibi: Abnormal areas show accumulation of an injected tracer. However, because MRI allows assessment of both kinetics and morphology, many lesions may be classed as nonmalignant with a high degree of assurance. Indeed, in a pro-

spective series, the false-negative rate was 4% (*5*). Localization is something of a problem, but MRI does let us accurately measure the distance to the lesion using skin landmarks; thus, lesions can be targeted with sonography or mammography once the location is known from the MR scan. Furthermore, localization devices that are under development will probably soon solve this problem. Like sestamibi, MRI also should not be used for screening or for avoiding biopsy. It seems now that the major use of MRI will be to stage known cancer or to search for sites of occult cancer in women at very high risk, such as those who are *BRCA1* or *BRCA2* positive.

From the body of the work of Khalkhali et al. (*1*), it is clear that a high proportion of breast tumors do accumulate sestamibi and that we can image them. However, the practical considerations discussed above have convinced me not to use it in my practice.

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REPLY: We note Dr. Shaffer's interest in our work (*1*) and his comments. We appreciate this opportunity to respond to his letter and clarify issues he has raised.

Shaffer presents his comments about our work in the context of 2 hypothetical groups of patients. Unfortunately, he seems to harbor misconceptions in both stages of his analysis. We believe it is most critical that the reader understand the objective of our study and that we correct the misperception underlying Shaffer's analysis of the first group of patients, those with mammographic or palpable abnormalities and hence those currently referred for biopsy. As stated in the article, the objective of our study was to determine the diagnostic accuracy for ^{99m}Tc-sestamibi breast imaging. Because tissue diagnosis is required to establish the performance of the test, we were ethically bound to study patients already scheduled for biopsy. Nowhere in our manuscript do we advocate that results from a ^{99m}Tc-sestamibi breast imaging study should be used to exclude a patient from biopsy.

As Shaffer builds his case against the use of ^{99m}Tc-sestamibi breast imaging in patients scheduled for biopsy (again, not a use proposed in our article), he analyzes a hypothetical group of 100,000 patients referred for screening, of whom he says 250 will have cancer (somewhat higher than the most recent age-adjusted incidence of approximately 120 reported by the American Cancer Society) (*2*). Though mammography is the best technique available for detection of breast cancer, Shaffer appears to overestimate its diagnostic sensitivity when he criticizes the ^{99m}Tc-sestamibi breast imaging sensitivity of 75.4% that we report. Recent reports for mammography in fact closely bracket our results for ^{99m}Tc-sestamibi breast imaging. One study defined a positive mammogram as one that led to a "recommendation for immediate work-up, such as additional imaging, obtaining prior images for comparison or biopsy" and reported 63% sensitivity for screen-film mammography (*3*). The second study defined a positive mammogram as one that required a recall for additional imaging studies or invasive procedures. Sensitivity varied as a function of recall rate, ranging from 65% to 80% (*4*).

Shaffer next considers the use of ^{99m}Tc-sestamibi breast imaging in patients with mammographically dense breasts. Again, he misrepresents the position of our study and presents the pitfalls of screening a hypothetical population of 100,000 women (not even restricting his analysis to women with mammographically dense breasts). We do not suggest the use of ^{99m}Tc-sestamibi breast imaging for screening but rather note in our article that it "may make a unique contribution in *selected* [emphasis added] populations." Appropriate application of new diagnostic technologies requires full validation through significant clinical experience and consideration of the pretest likelihood of disease in a specific population.

Shaffer also expresses concern about the challenge of localizing abnormalities detected by ^{99m}Tc-sestamibi breast imaging that are not detected by mammography. Some of those lesions can be retrospectively detected by mammography and some by sonography. Additionally, 2 research groups have published techniques for scintigraphic localization (*5*,*6*).

We believe that ^{99m}Tc-sestamibi breast imaging should be used selectively and will continue to be useful to the clinician faced with a diagnostic dilemma. Just as Shaffer has suggested that MRI will be used for patients at high risk, ^{99m}Tc-sestamibi breast imaging represents a cheaper and more widely available tool for the same population.

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