SCINTIMAMMOGRAPHY: MAGIC BULLET OR FALSE PROMISE?

News reports have declared that a nuclear medicine scan for breast cancer may soon replace biopsies. But could too much publicity too soon stop the test in its tracks?

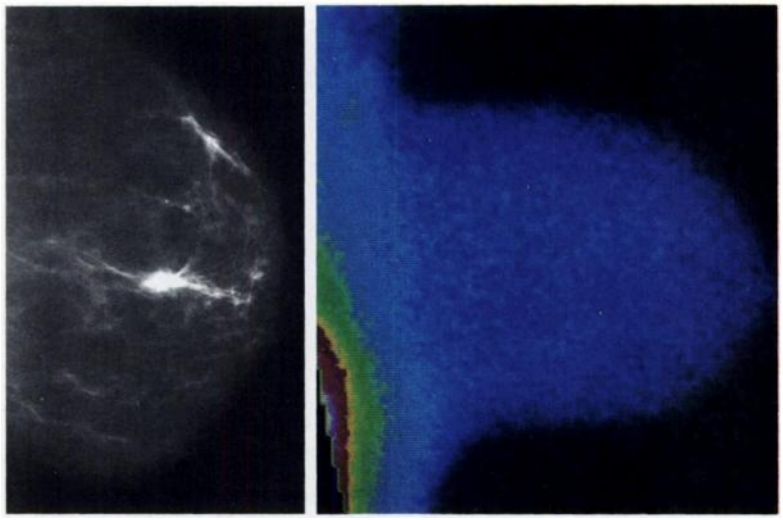
SEVERAL WEEKS AGO, NUCLEAR medicine made front page headlines when researchers announced that scintimammography could prevent the need for unnecessary biopsies in women suspected of having breast cancer. The test using the imaging agent ^{99m}Tc-sestamibi was shown to be 90 percent effective at detecting tumors in women who had palpable and nonpalpable lesions on their mammograms, according to Iraj Khalkhali, MD, an associate professor of radiologic sciences at UCLA School of Medicine in Los Angeles. He concluded that the experimental test could eventually replace many biopsies saving the country millions of dollars in medical bills. More than a dozen major newspapers and the news on all three TV networks carried the story. Since the recent publicity, Khalkhali has received over 400 phone calls from women with breast lumps who want to have the nuclear medicine imaging procedure.

The brouhaha over this experimental test has stirred a great deal of debate among nuclear medicine physicians: Many applaud the news reports which portray nuclear medicine in a positive light. Others are concerned that the press reports are premature and that Khalkhali's findings may not pan out in two multicenter trials that are currently underway. Some physicians have been exchanging their comments and concerns about scintimammography back and forth on Loyola University Nuclear Information System (LUNIS), the nuclear medicine computer bulletin board. Yet they have not reached a general consensus about whether the press coverage will further scintimammography along or impede its widespread use by creating false hopes.

The Need for a Better Imaging Test

The reason why the media has been eager to promote scintimammography is because standard mammography has been shown to have major limitations. Many breast cancer experts believe that a better diagnostic imaging tool is needed given that an estimated 700,000 breast biopsies are done every year with only 1 in 4 finding cancer. Scintimammography, which employs radionuclides that have a high uptake in breast cancer cells, is thought to have a much higher positive predictive value than mammography.

Indeed Khalkhali's findings, which he presented at the Radiological Society of North America's annual meeting in November, were promising: In his study, 147 women with breast lesions that warranted biopsies were injected with sestamibi (20mCi) ; their breasts were imaged in the prone lateral position (to get a better image and decrease background radiation from other organs) with a high-resolution digital camera at 5 and 60 minute intervals. Evaluating a total of 153 suspicious lesions, scintimammography correctly identified cancer in 90 percent of cases—with a 7 percent false-positive rate and a 3 percent false-negative rate. (Mammograms have a 70 to 85 percent false-positive rate and a 10 to 15 percent false-negative rate.)



(Left) Mammographic results indicate possible carcinoma. (Right) Normal scintimammograph in the lateral prone position. Later biopsy revealed benign fibrocystic disease.

"I was very impressed by these results," said Stephen Larson, MD, chief of nuclear medicine at Memorial Sloan-Kettering Cancer Center in New York. "If the findings are replicated in the multicenter trials, I think nuclear physicians will begin to do this test immediately. Most hospitals already have the equipment, and the public demand for it is high." While some scintimam-

A Tracer Improves Mammograms

CHICAGO, Nov. 29 (AP) — A radioactive tracer injected into women who may have breast cancer has been 90 percent effective in identifying malignancies without a painful biopsy, researchers say.

The experimental technique, used after mammograms raise cions, could take the bior res ann Soci "M at de the b four o on a n cancer

The method could

more than 600 women at Harbor-U.C.L.A. Medical Center, where he is chief of breast imaging. He repo d on 147 consecutiv

Test finds breast cancer without biopsy

STUDY FUELS MAMMOGRAM DEBATE, 1D

By Marilyn Elias
USA TODAY

An injection that makes breast cancers "light up" in photos taken with a high-tech camera could save thousands of U.S. women from biopsies every year, a scientist says.

about 1 in 4 finds cancer, Iraj Khalkhali of UCLA Medical School said Monday.

These surgeries could be sharply reduced by using a nuclear medicine technique that identifies cancer in 90% of cases otherwise requiring biopsies, he told the Radiological Society of Nor merica

active tracer. Then a nuclear "detector" camera takes images of the breast. The radiation dose is about equal to that received on a cross-country plane flight, Khalkhali says. "This shows

In his study of 147 women who got standard biopsies and the nuclear medicine photos, 7% would have received "false positives" from radioactive tracers — a cancer diagnosis

be cancerous but weren't identified as malignant by the tracers. Three of these women had lesions between the ribs.

A newly designed camera seems to be reaching this area better, says Khalkhali.

Biopsies cost $1,500-$5,000; the new test runs $600. Clinical trials on the technique are un-

negatives: le- identified by the technique that turned out to be cancerous, he said.

Among the four false negatives, three involved women with lesions between ribs. A newly designed cam- eem to reach that area better

Khalkhali, an ould rec on a cross ntry

disease. The patient is exposed to about the same amount of radiation

mography researchers are encouraged by the test's positive predictive value, others are concerned that its false-negative rate is too high for it to be beneficial in the general population. "Breast surgeons at my institution would like to see a lower false-negative rate before they utilize scintimammography," said Robert Henkin, MD, professor of radiology and director of nuclear medicine, Loyola University Medical Center in Maywood, IL who is participating in the multicenter trials. "Otherwise, the test would miss too many cancers."

Khalkhali contends that the false-negative rate is largely due to the limitations of gamma cameras: Three of the four false-negatives in his study were in the medial part of the breast in between the ribs, which is out of the detector's range. He said the problem should be solved by using gamma cameras dedicated to breast imaging. Also, Khalkhali indicates he is aware of at least one nuclear medicine company that is developing a new gamma camera equipped with a semiconductor instead of a scintillator and vacuum tubes. The semiconductor camera may eliminate the problem of dead space which is typical in traditional gamma cameras. It is also much smaller and lighter, so it can be rotated more readily for multiple views of the breast, resulting in improved resolution.

Dupont's Clinical Trial: Did Publicity Help or Hurt?

In the shadows of the current press coverage, Dupont Merck Pharmaceutical Company in Billerica, MA is funding two large scale clinical trials of scintimammography using ^{99m}Tc-sestamibi, which it markets under the tradename Cardiolite. In fact, it was Khalkhali's earlier studies using sestamibi for breast imaging that prompted the company to sponsor the trials of Cardiolite, which is approved by the Food and Drug Administration for heart imaging. Researchers (including Khalkhali) from 55 institutions across the U.S. and Canada are performing scintimammography on 600 women who have either a palpable mass or a finding on a mammogram that warrants a biopsy. The scintimammography results will then be compared with the patients' biopsy findings to assess if the test has a high predictive value.

Before the news splash, women were enrolling in the trials at a snail's pace: Although the trials opened last April, less than half of the enrollment slots had been filled by November. "Women who were told they needed a biopsy were reluctant to enter a clinical trial for a test they had never heard of," said Judith Murphy, MD, medical director of Dupont Merck. The good news is that the enrollment rate has nearly doubled since the press reports. "We're hoping that women who are now approached have heard about this scan in the news, have a positive impression of it and are more willing to enter the studies," said Murphy.

While Murphy acknowledges the assets of publicity, she also worries that some women may have been misled by the inflated news coverage. "Patients may have misinterpreted the news to mean that this test has a proven efficacy as a diagnostic tool and is available in clinical settings—which just isn't true," she said. She emphasizes that Khalkhali's results are not necessarily predictive of what the upcoming trial will find.

The trials are slated to be completed by the end of this year. If the findings are encouraging, Dupont Merck will submit them to the FDA for review to see whether Cardiolite's package insert can be expanded to include breast imaging. "At this point, concluding that the test is efficacious is premature," said Murphy. "The press coverage is based on preliminary evidence from one institution."

Should Researchers Play Up to the Press?

Although some in the nuclear medicine community think the press coverage on scintimammography has been premature, Khalkhali disagrees. He feels the news reports have helped the field of nuclear medicine by improving public awareness. In fact, Khalkhali made an effort to get media pickup by presenting his findings in media-friendly language. "I used the words 'radioactive tracer' instead of 'drug' to describe sestamibi," he said. He also came up with a way to minimize the radiation that a patient receives from a nuclear scan: "I said it was equal to the amount of radiation a

person gets when they fly roundtrip from New York to Los Angeles."

Many nuclear physicians oppose Khalkhali's tactics and are concerned that the press acted irresponsibly by hailing an experimental imaging tool as a magic bullet. If the data from the multicenter trials aren't as strong as Khalkhali's, experts fear the publicity could backfire. Scintimammography may be branded "a letdown" before researchers even identify which subset of women can benefit from it. For these reasons, some physicians contend that scintimammography should have remained cloistered within the research community until the forthcoming trials can provide more definitive answers. "While I don't fault Khalkhali for presenting his abstract at a public forum," said Henkin, "I think it's a bad idea to overpromote something before the research is in. There's definitely been too much media hype too soon. If it fails, the nuclear medicine community will be portrayed in a bad light."

Until the RSNA meeting, the research presented on scintimammography over the past decade (using Sestamibi, ^{201}Tl, ^{18}F FDG and other radionuclides) has remained out of the media spotlight. In fact, four abstracts on this topic—including one by Khalkhali similar to his most recent study—were presented at the Society of Nuclear Medicine's (SNM) 1994 Annual Meeting last June.

The widespread press coverage may have been generated at the RSNA meeting—not because of any major advances in the research—but because of logistics. Khalkhali was coached for several hours by public relations executives hired by RSNA on how to present his findings for a mass audience. (SNM doesn't provide such a service for its presenters.) Moreover, RSNA distributed a press release to more than 700 media organizations that emphasized the major impact that scintimammography could have both in terms of reducing the number of disfiguring and invasive biopsies and saving millions of dollars in medical costs. The release cited the differences in cost between the "$1500 to $3000" biopsy and the "$600" scintimammogram, which were quoted in most of the news articles.

While nuclear physicians wrangle over whether preliminary research findings should make national news, they may still need to face the reality that publicity can bolster research grants and academic prestige. As federal grant money dries up, many researchers are turning more and more to private corporations and investors to fund their studies. Since the headlines, Khalkhali said his prospects for grants have soared. He has received several calls from Wall Street investment companies and private corporations interested in funding his work and investing in the experimental semiconductor camera. "Investors recognize that there's an incredible demand for scintimammography," he said, "both among women who are told they need a biopsy of breast tissue and with insurance companies that have to pay for all these unnecessary surgeries."

Although publicity may have its payoffs, it often has a price—namely misinformation. A short newspaper article or 60-second soundbite on the evening news can't possibly provide patients with the information they need to put the research into perspective. What's more, the media tends to exaggerate new findings in an effort to play up the news. This problem is not unique to nuclear medicine. A few years ago, the press reported that mammograms may actually *cause* cancer when the preliminary findings from the Canadian mammography study found an increase in cancer mortality among women under 50 who were screened. More recently, headlines have declared that everything from vitamins to hot dogs to chili peppers causes cancer.

As a result of the scintimammography coverage, many women have been calling hospitals to find out where they can have scintimammography

Who Could Benefit from Scintimammography?

While scintimammography undergoes extensive review in the research setting, nuclear physicians ponder who will benefit from the test if it becomes clinically available. All the researchers agree scintimammography won't replace mammograms as a screening test in the general population. And most believe it will be useful for some patients. However, no one knows how to decide which women should have the test. Alan Waxman, MD, a scintimammography researcher and director of nuclear medicine at Cedars-Sinai Medical Center in Los Angeles outlines the possibilities:

- **Women with dense breasts:** These women have a much higher rate of false-positives and false-negatives on screening mammograms than women with fatty breasts. Scintimammography may be an effective alternative for screening women with dense breasts. The trouble is how to determine the criteria for whether a woman has dense breasts. Also, researchers still don't know how well scintimammography distinguishes between carcinomas and benign fibroadenomas.
- **Young women at high risk for breast cancer:** Those who have a family history of premenopausal breast cancer, radiation treatments to the breast or a prior history of breast tumors may benefit from having scintimammography as a screening test when they're in their thirties or forties.
- **Women with palpable lumps or abnormal lesions on their mammograms:** Scintimammography may be useful for determining if these abnormalities warrant further evaluation through biopsies. "But we've found that lesions smaller than 8 mm are impossible to detect on scintimammograms, and those between 8 and 15 mm have only a 50 to 60 percent sensitivity," said Waxman. "So women who have malignant calcifications may wind up with missed cancers."
- **Patients with breast cancer:** Women with breast cancer who are deciding between a lumpectomy and mastectomy may benefit from scintimammography since it can pick up multicentric disease which requires treatment by mastectomy.

since they haven't gotten the message that the test is still experimental and not widely available. "A lot of my friends and relatives misinterpreted the news reports to mean scintimammography was going to replace mammography as a screening tool," said Henkin. At the extreme, some patients now think they don't need to have a lump evaluated via a biopsy since it probably won't turn out to be cancer. Khalkhali concedes that he's received "about 5 or 6 calls from surgeons complaining that patients have been canceling biopsies as a result of this publicity."

When Patients Demand Experimental Procedures

Fielding calls from women across the country, Khalkhali has encountered the public's response to the news reports first hand. Most of his callers are scheduled for breast biopsies and want to have scintimammography instead. "I explain to them that scintimammography is still experimental, and I usually encourage them to enroll in the multicenter trials that Dupont Merck is sponsoring," Khalkhali said. However, many women are disconcerted to learn that even if they enroll in a trial and get scintimammography, they'll still have a biopsy. (The trials aren't designed to use a negative scintimammography result as a substitute for a biopsy.)

For these reasons, some callers have opted not to become research subjects and about 30 women have actually traveled to California and have paid $600 out of their own pockets to have Khalkhali evaluate their breast lesions with scintimammography. "If the result is positive, I tell the patient she definitely needs a biopsy. If it's negative, I spend a lot of time explaining to her that this test is experimental and that she could be taking a grave risk by delaying a biopsy. I also always send my report to the patient's surgeon and primary care physician."

As head of the breast imaging center at Harbor-UCLA Medical Center in Torrance, Khalkhali reads 40 to 50 mammograms a day and is qualified to render a judgement based on a woman's mammogram and scintimammogram results. However, many researchers are concerned that the high demand for this test generated by the press will encourage some physicians to start doing scintimammograms on their own before the trials are complete. Although insurance companies won't cover the test since it is experimental, many women (as Khalkhali can verify) are willing to pay for it themselves. "This could go the way of the renal scan," said Henry N. Wagner, Jr., MD, professor of medicine, radiology and environmental sciences at The Johns Hopkins Medical Institutions in Baltimore. "When it first was developed in the 1950's, doctors who weren't trained to do it started performing it and misinterpreting the results. For several years, the test was thought to be a failure until it was correctly administered." While nuclear physicians eagerly await the verdict on scintimammography, many hope that history won't repeat itself.

Deborah Kotz

Institute of Medicine Urges Construction of New Accelerator

An influential report bolsters support for the proposed National Biomedical Tracer Facility, but downplays the need for U.S. production of molybdenum-99.

ALTHOUGH THE SUPPLY OF RADIONUCLIDES meets current commercial demand, the United States government needs to take steps to stay competitive with other countries and to ensure that future demand doesn't outstrip supplies. This includes building and funding the year-round operation of a new particle accelerator for the production of radionuclides, concludes a long-awaited report on isotope supply released in December by the Institute of Medicine, a division of the National Academy of Sciences in Washington, DC. The report, titled *Isotopes for Medicine and the Life Sciences*, stated that the Department of Energy (DOE) should create a National Biomedical Tracer Facility (NBTF) for the production of radionuclides that are not available from commercial suppliers. It said the facility "is essential for the United States to maintain continued leadership in biomedical research using radiotracers."