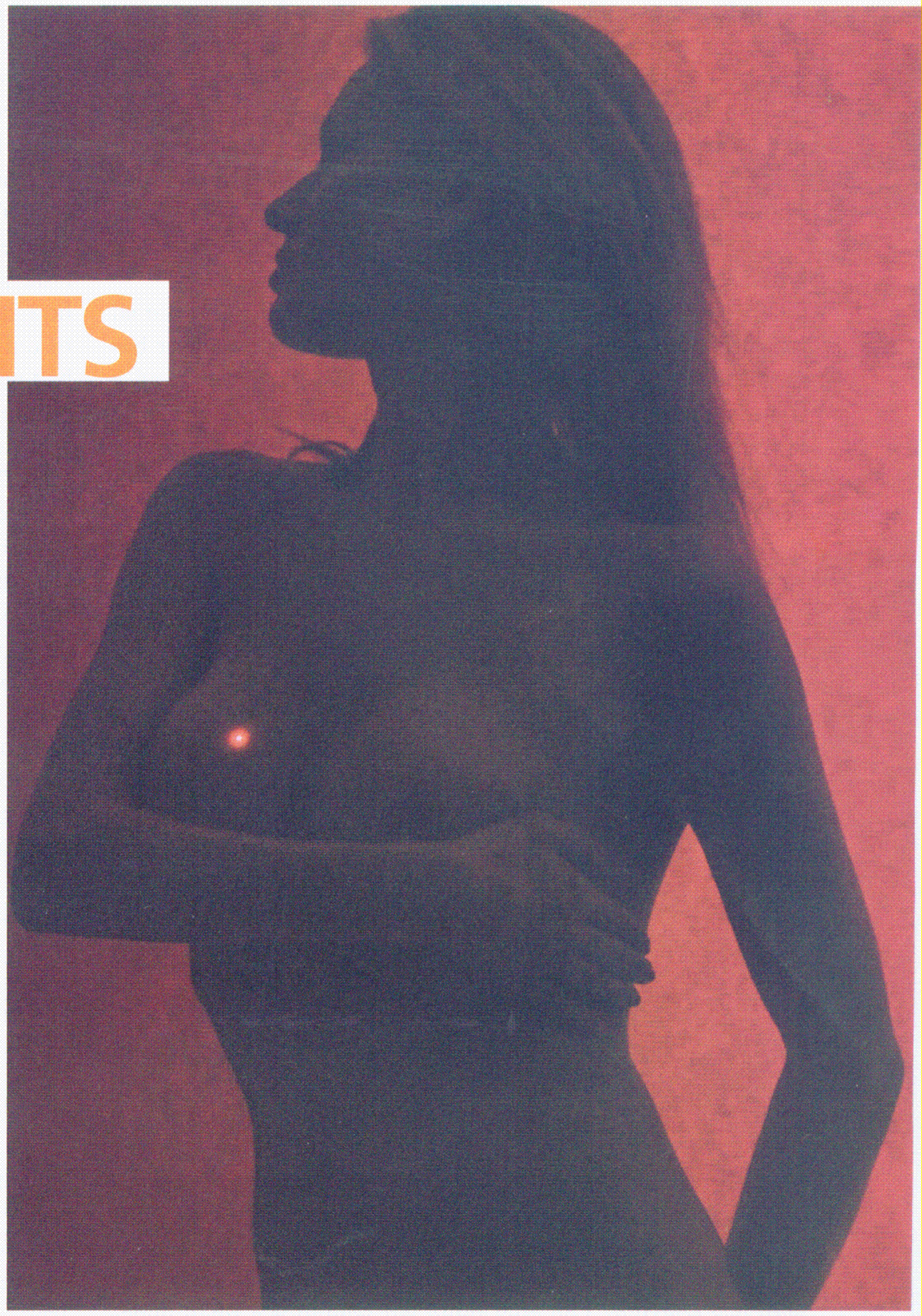
KINDER, GENTLER TREATMENTS FOR BREAST CANCER

Doctors are on the verge of determining which localized tumors will remain slow-growing, and which will become aggressive killers—and treatment will be revolutionized

By Kathleen McAuliffe



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The days when mastectomies were routine are mercifully gone. But breast-cancer therapy can still be painful, protracted and disfiguring—and more doctors are acknowledging that, for many women, the cure can sometimes be worse than the disease.

This can be true for some breast cancers caught at the localized stage (meaning they have not broached the lymph nodes, a sign they have spread). These now constitute the majority—62 percent—of the estimated 203,000 breast-cancer cases diagnosed last year. It's even more poignant for the additional 54,000 women whose malignancies were caught so early that the minute cluster of cancerous cells had yet to break through the milk duct, a condition known as ductal-cell carcinoma in situ, or DCIS. Doctors widely acknowledge that some localized cancers might be cured with surgery alone, sparing women radiation and chemotherapy; it might be possible one day to leave certain cases of DCIS in a woman's breast without endangering her. "In general, more women die *with* DCIS rather than because of it," says Julie Gralow, M.D., associate professor of medical oncology at the University of Washington in Seattle.

The problem is that, right now, no one knows which patients will be fine with less treatment. In fact, new data suggests that tumor size and lymph-node involvement are not as powerful prognostic indicators as once thought. Small tumors can spread and kill, while large ones may stay localized. And left untreated, DCIS may evolve into an invasive cancer that can spread. Lacking a crystal ball, doctors must treat all cancers, no matter how tiny, as if they have the potential to be lethal. After surgery to remove the tumor, radiation is often recommended to reduce the risk of recurrence. If tests give any hint the cancer may behave more aggressively, surgery is typically followed by chemotherapy or other drug regimens notorious for their debilitating side effects.

But that could soon change. Now available, or in advanced testing, are treatments that promise to be less lengthy and minimize scarring. Better yet, medical

researchers are rapidly developing molecular tools for predicting which tumors are likely to spread—which means doctors may one day be able to reserve the heavy artillery for more dangerous tumors, sparing many women harsh interventions. To be sure, more research is needed on these approaches, but experts are hopeful that better treatment options and easier choices for women are on the horizon.

MINIMALLY INVASIVE BIOPSIES

Seventy to eighty percent of biopsies come back benign. But all too often, finding out whether a suspicious lump is cancer has meant in-hospital surgery and a one- to two-inch scar. Now, a less invasive outpatient procedure, available at many teaching hospitals, cancer-care and breast-care centers and large private hospitals, allows women to obtain accurate results without general anesthesia or stitches. The new approach replaces the scalpel with either a fine needle, core biopsy needle or a thin vacuum probe no bigger than a pencil. Using X rays or ultrasound for guidance, the instrument is inserted into the suspicious site and tissue removed by either a spring-loaded device or a vacuum-assisted apparatus called a Mammotome. The latter is typically recommended if the target is not a clearly defined mass or consists of calcifications, as several samples can be acquired with a single insertion.

Numerous studies show that the core-needle and Mammotome yield diagnoses just as accurate as a surgical biopsy, but with less scarring. The only thing left behind is a small puncture, reports Joshua Gross, M.D., chief of the division of breast imaging at Beth Israel Medical Center in New York City. If a woman has cystic breasts, calcifications or other conditions that may necessitate multiple biopsies, the advantage of a slim probe over the scalpel mounts. "I frequently see women whose breasts are distorted and crisscrossed with scars from surgical biopsies, and yet they didn't even have cancer," Gross says. "With the tools now available, detecting disease doesn't have to be so damaging."

GENETIC FINGERPRINTING OF TUMORS

In what scientists hailed as a landmark study last December in *The New England Journal of Medicine*, Dutch researchers reported exciting progress toward developing a test to predict which breast cancers will spread. Using microarrays (specialized chips that bind to genetic material), they screened breast tumors for activity of multiple genes and uncovered 70 genes that looked promising for predicting patient outcomes. They then examined breast tumors from 295 mostly middle-aged women whose disease was confined to the breast or had spread no farther than the underarm lymph nodes. Among patients for whom the genetic test predicted a good prognosis, 85.2 percent remained cancer-free ten years later, as compared to 50.6 percent of women given a poor prognosis by the test.

The genetic signature appeared to be superior to traditional criteria for predicting outcomes, such as the size of the tumor, how it looks under a microscope, number of lymph nodes affected and estrogen receptors. Indeed, small tumors often had bad prognoses and large tumors good prognoses.

"The hope is this kind of molecular fingerprinting of tumors will help us identify who needs much less aggressive treatment," says Todd Golub, M.D., who directs cancer genomics research at the Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts. "It may be that some tumors we're currently treating with chemotherapy or radiation could be cured with surgery alone." In the case of DCIS, he says, it may even be possible to do nothing at all for carefully selected patients.

He and other scientists caution that the prognostic accuracy of genetic fingerprinting is not yet powerful enough for doctors to recommend withholding therapy. But with many pharmaceutical companies and academics studying the technology, rapid advances are widely anticipated.

"In the next four to five years, these arrays will be in wide clinical use and will transform cancer diagnosis and management," says Marc Lippman, M.D., a breast-cancer expert and chair of the department of internal medicine at the University of Michigan Medical School. Another way the technology might potentially be deployed, he says, is for women at high risk for recurrence to get treatment tailored to the genetic underpinnings of their disease. "We have about one hundred anti-cancer agents that all affect different tumor-growth pathways," he says. "These arrays should enable us to go straight to the drug, or combination of drugs, that will be most effective."

Within five years, genetic tests will transform cancer diagnosis and management.

NONSURGICAL LUMPECTOMIES

Using radio-frequency energy, lasers and freezing methods, it's possible to destroy tumors from the inside, without cutting open the breast. This promises far superior cosmetic results and faster recuperation times. These slice-free techniques are still in clinical testing, but if successful, could be offered on an outpatient basis to many women who currently qualify for a surgical lumpectomy.

Some of these methods could be clinically available as soon as five years from now, says Eva Singletary, M.D., professor of surgical oncology at Houston's University of Texas MD Anderson Cancer Center, which recently participated in a multicenter trial of radio-frequency energy. In the study, doctors used ultrasound to guide a needle into the tumors of 30 patients. Once it's properly inserted, prongs splay out from

PHOTO: DARRYL ESTRINE.

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the tip of the needle and begin vibrating, causing frictional heat that cooks the tumor from the inside. To test the effectiveness of the procedure, all the patients then received either a lumpectomy or a mastectomy, and the tissue was examined for signs of cancer. Except for four patients (including two in whom the probe could not be accurately placed), "We're seeing one hundred percent destruction of the cancer cells," says Singletary. "There's a lot of enthusiasm about this." In her next trial, women treated by the technique will be able to forego a lumpectomy or mastectomy afterward, but multiple needle biopsies will monitor for the presence of cancer cells.

Meanwhile, at Rush-Presbyterian-St. Luke's Medical Center in Chicago, similar advances are being reported by Kambiz Dowlat, M.D., and colleagues using a thin fiber-optic cable inserted into the breast to zap tumors targeted with a laser. Still another group is making progress using a pencil-thin probe to pierce the breast and freeze the tumor with argon gas.

To date, these methods have produced almost no side effects, save for one minor skin burn. Nonetheless, not all women will be good candidates. In general, experts say nonsurgical approaches work best with small tumors that can be seen clearly on a mammogram; when heating methods are used, tumors cannot be close to the surface of the skin or chest muscle.

RADIATION: SHORT AND SWEET

Radiation after a lumpectomy reduces the risk of a local recurrence by 10–30 percent, but it can be an ordeal. Five days a week, for six and a half consecutive weeks, women must go to the hospital—a big inconvenience for working women and those who have to drive long distances to obtain treatment. That drawback sent doctors looking for a swifter way to achieve the same outcome, and new findings suggest they're succeeding. In patients who had small tumors that were completely removed, early data indicates that radiation can be compressed into less than a week without increasing the risk of relapse. What's more, these patients are less likely to suffer such common side effects as fatigue, redness and unwanted radiation exposure to healthy surrounding tissues.

"The vast majority of tumors come back right where they used to be," says Robert Kuske, M.D., professor of human oncology at the University of Wisconsin in Madison. By focusing radiation only at the site where the risk of recurrence is greatest, he says, it's possible to shorten treatment.

Using a treatment similar to brachytherapy for prostate-cancer patients, Kuske numbs the breast with local anesthesia and then guides 12–30 thin catheters around the lumpectomy site. A tiny radioactive seed is run down into the tip of each and treatment delivered for ten to fifteen minutes twice daily for a total of four to five days. (The catheters remain in place during this time.) For nearly twelve years, Kuske has used this procedure to treat approximately 350 patients—so far, with excellent results. After an average of six years, his patients have actually had a slightly lower rate of recurrence of cancer than would be expected in the same period with standard radiation. Most local recurrences appear within the first five years; Kuske plans to track all patients for a full ten years. ▶

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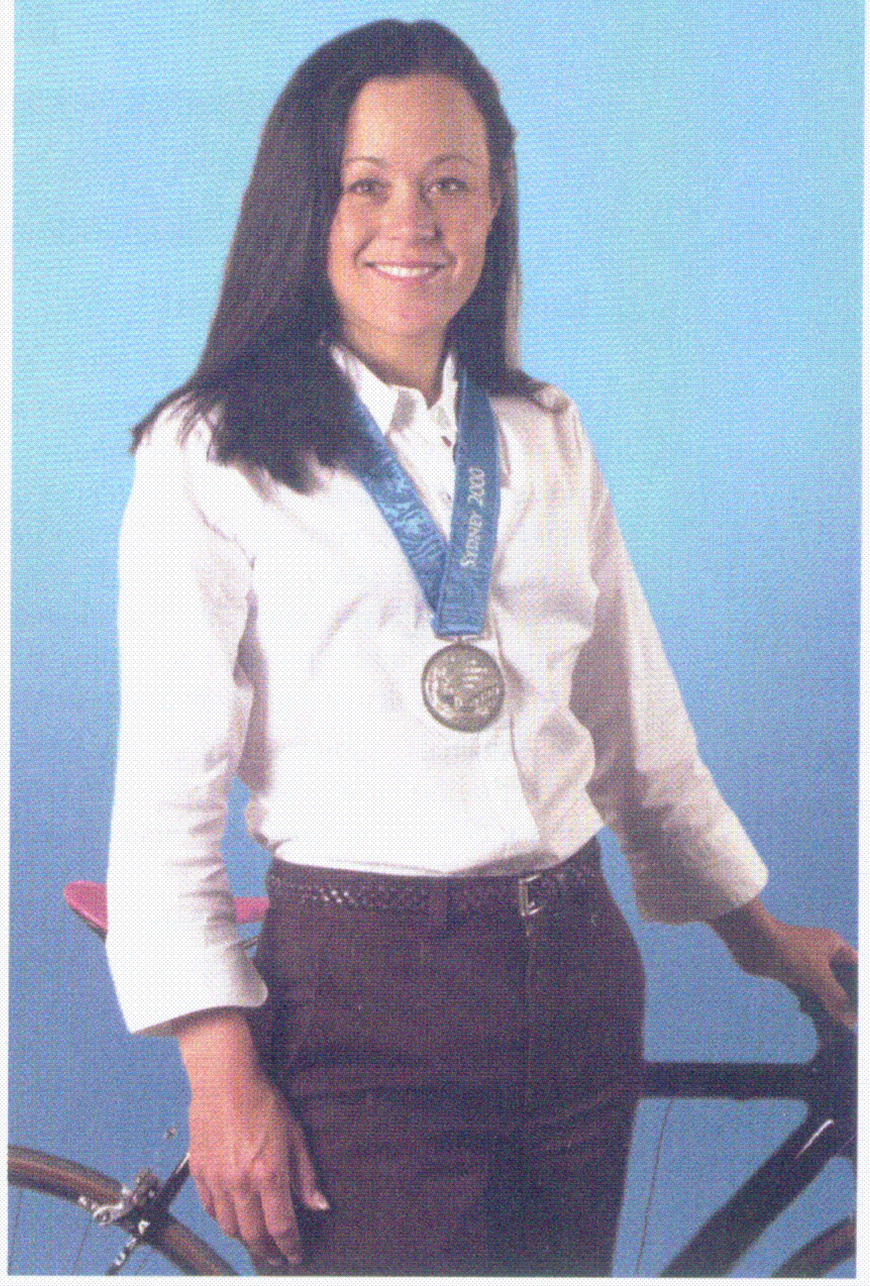

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To deliver brachytherapy to the breast more efficiently, Kuske and other doctors are now employing a recently approved device called MammoSite. It consists of a single catheter tipped by a balloon that holds the radioactive seed. For appropriate patients, say experts, the device is a lot easier to insert than multiple catheters, and requires a single small incision; treatment lasts about the same amount of time. So far, however, MammoSite patients have only been followed for two and a half years.

Another timesaving alternative to the standard six-and-a-half-week radiation regimen—and one that has the further advantage of being totally noninvasive—is being developed by Silvia Formenti, professor and chairman of radiology oncology at New York University School of Medicine. With her approach, the patient is placed on her stomach on a table with a hole through which the breast drops down. Instead of radiating the whole breast, a higher than normal dose of radiation is focused only on the area at highest risk of a recurrence. In this way, treatment can be completed in five 15-minute sessions given every other day.

Ideally, women who get partial breast radiation with seeds or an external beam should enroll in clinical trials, says Formenti, and have a tumor no bigger than three centimeters in diameter and no or minimal lymph node involvement.

Until further studies are completed, however, the treatment's long-term effectiveness cannot be guaranteed. Indeed, there are concerns that the strategy would not protect women with unsuspected multifocal disease, or clusters of cancer cells in more than one part of the breast, reports LaMar McGinnis, M.D., senior medical consultant at the American Cancer Society.

The hope is that genetic science will one day identify cancers likely to be multifocal, enabling doctors to select patients most likely to benefit from shorter, more focused regimens. "Currently, many women who are ideal candidates for a breast-conserving lumpectomy are instead choosing a mastectomy owing to the time and hardship of getting conventional radiation," says McGinnis. "Faster, more convenient treatment would likely change their choice." ■