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THE SCIENCE OF CAVE FORMATIONS



ULTRASOUND'S NEW FOCUS

Can it eradicate tumors?

BY BEN HARDER

The Dominican Republic is known among tourists for its white sands, magnificent waterfalls, and unusual wildlife. But none of those was the attraction that drew Charles A. Reinwald. He came for a rendezvous with an ultrasound device. Reinwald had aggressive prostate cancer, and he didn't care for the treatment options available in the United States. So, one day in late June 2004, Reinwald traveled from his home in Tequesta, Fla., to a hospital in the Dominican city of Santiago. There, a Miami-based urologist directed ultrasonic waves at the patient's cancerous prostate gland.

The Dominican Republic and various other countries, including Canada, England, and Mexico, permit doctors to treat prostate cancer with a technique called high-intensity focused ultrasound, or HIFU. It often avoids the irreversible side effects, including impotence, that can arise during surgery, radiation, and the other treatments available in the United States.

In the Santiago hospital, urologist George Suarez and his assistants inserted a transducer emitting ultrasonic waves into Reinwald's rectum. The curved transducer put the waves on converging paths in the same way that a magnifying glass focuses sunlight. Where the streams of energy intersected at the prostate, the temperature soared to more than 80°C, cooking small batches of tumor cells in seconds.

For about 2 hours, the transducer steadily shifted its aim across rows of space. Its progress resembled that of a dot matrix printer applying ink to paper. Tissue just millimeters away from the HIFU target zone remained unharmed.

Reinwald's cancer isn't cured, but he hasn't required medical intervention since the operation. At age 80, he works full-time as president of the Cancer Cure Coalition, a nonprofit organization that he founded in 2000 after his wife's diagnosis of cancer.

He expresses no regrets about his HIFU treatment. "Why do [surgery] when I have available to me a less toxic treatment?" he asks.

HIFU, however, is not generally available in the United States. It has been approved for only one use: treating uterine fibroids. Suarez and other urologists who treat U.S. men who have prostate cancer do so abroad and charge about \$20,000 per case. Patients also need to pay their own way to Santiago, Toronto, or another foreign city to undergo the procedure.

A handful of companies market HIFU devices. Although they vary in design and therapeutic purpose, all the machines rely on the same underlying principle. They focus ultrasound energy at a point several centimeters away from the transducer and destroy tissue there.

The companies, including US HIFU of Charlotte, N.C., which Suarez partially owns, have funded research to test whether the

new approach is safer and more effective for a variety of cancers than standard therapies are. Breast, bone, brain, and liver tumors are among those cancers being treated experimentally with HIFU. Investigators also continue to study the efficacy of the technique in women with fibroids. In each case, physicians must place the transducer within a few centimeters of the target.

While HIFU appears to sidestep some typical side effects of surgery and radiation, it's not yet clear whether the novel approach is as successful at curing cancers as those standard treatments are. So far, no study has directly compared the ultrasound procedure to an established cancer treatment.

A British government body, the National Institute for Clinical Excellence, maintains that the evidence "appears adequate to support the use of this procedure for prostate cancer." But it also states in a document that offers guidance to the National Health Service, "The effects of HIFU for prostate cancer on quality of life and long-term survival remain uncertain."

FIXING FIBROIDS Uterine fibroids are nonmalignant tumors that can impair fertility and sometimes cause pain, heavy menstrual bleeding, and urinary frequency. The condition has traditionally been treated by surgical removal of the uterus, or hysterectomy. This approach definitively rids a woman of fibroids and relieves the pressure that the fibroids had placed on nearby tissues.

In contrast, HIFU "does not totally get rid of the fibroids," says radiologist Fiona Fennessy of Brigham and Women's Hospital in Boston. "This isn't a malignant tumor. All we're trying to do is improve symptoms."

To minimize risks such as skin burns and damage to healthy internal tissues, radiologists destroy only the center of the fibroid and don't attempt to heat the surrounding area, called the margin, Fennessy says.

However, because the blood vessels that support a fibroid are concentrated near its core, destroying the center usually eliminates part of the margin, says gynecologist Phyllis Gee, director of the North Texas Uterine Fibroid Institute in Plano.

To evaluate HIFU's success, Brigham and Women's researchers led by gynecologist Elizabeth A. Stewart treated more than 100 women who had fibroids. The team used a machine made by InSightec Ltd. of Haifa, Israel, that incorporates an ultrasound transducer into a magnetic-resonance (MR) scanner.

During treatment, a sedated woman lies facedown on the bed of the scanner. Beneath her abdomen, the ultrasound transducer aims and fires away for up to 3 hours while the MR scanner lets doctors monitor tissue temperature and fibroid position.

Most patients experience a "mild level of pain" during and immediately after procedure, Stewart says.

"There's a sense of urgency. [Prostate cancer] is the most common cancer in men."

— GEORGE SUAREZ, M.D.
MIAMI, FLA.

Stewart's team reported in the January *Fertility and Sterility* that 71 percent of the patients treated have a significant reduction in fibroid symptoms for at least 6 months, and 51 percent experience that improvement for at least a year. HIFU doesn't produce sufficient relief for all women, however. Seventeen percent of the volunteers sought another treatment, such as hysterectomy, within a year, Stewart says.

Women treated with HIFU missed an average of 1.4 days of work after the operation, Stewart says. That compares with 18.9 missed days among women treated by hysterectomy for similar fibroids, Stewart reported in Jerusalem last June to the Israel Society of Obstetrics and Gynecology.

To measure the benefit 3 years after treatment, Gee is leading a new study that will track 70 women with fibroids who received HIFU. InSightec funded both studies.

After reviewing preliminary clinical data, the U.S. Food and Drug Administration in late 2004 approved the InSightec equipment for clinical use in treating fibroids.

SOUNDING OUT MALIGNANCIES

Unlike fibroids, malignant tumors need to be rooted out entirely if they're to be beaten. In surgery, doctors remove a specific amount of surrounding healthy tissue to avoid leaving behind any cancer cells. Similarly, in HIFU, doctors may need to kill a veneer of healthy tissue around each tumor, concluded Moshe Papa and Douglas Zippel of Sheba Medical Center in Tel Hashomer, Israel, in the January 2005 *Breast Cancer*.

Those researchers used HIFU to treat 10 women who had breast cancer and were planning to have partial mastectomies. After the procedure, the investigators removed a portion of each treated breast to see whether HIFU had eliminated the tumors. Two volunteers showed no sign of remaining cancer, but eight patients retained at least some cancerous cells at the tumor site.

Feng Wu and his colleagues in Chongqing, China, have taken a more aggressive approach. Between 1998 and 2001, they administered HIFU—in combination with either surgery or chemotherapy—to 45 women with breast cancer. They intentionally destroyed a 1.5-to-2-centimeter-thick layer of normal tissue around each tumor.

Five years later, 89 percent of the women had had no recurrence of disease, Wu reported last December at the Radiological Society of North America meeting in Chicago. Wu holds stock in the company that makes the device that his team tested. The study didn't include a comparison group of similar patients receiving a conventional treatment.

In other studies, it's not uncommon to find that after surgery and radiation therapy, more than 90 percent of volunteers who have breast cancer go at least 5 years without recurrence.

InSightec-sponsored researchers have begun a trial of HIFU in treating breast tumors and surrounding breast tissue in 200 women in Germany and Japan.

The cosmetic side effects of HIFU are minimal. Since HIFU doesn't break the skin, it rarely disfigures the breast, Wu says.

David Gianfelice of Toronto General Hospital, one of the first North American researchers to use HIFU in breast cancer treatment, notes that third-degree skin burns have resulted in some cases. But recent refinements to the InSightec hardware have minimized that problem, he says.

By delivering "a nice, tight package of heat" to the tumor, MR-

guided HIFU might eventually supplant surgery as the treatment in some cases of breast cancer, Gianfelice says.

That same goal applies in prostate cancer, which researchers abroad have been treating with HIFU since the mid-1990s. For example, more than 400 men with early-to-mid-stage prostate cancer have received HIFU as an initial therapy using the device manufactured by EDAP of Vaulx-en-Velin, France.

Andreas Blana and his colleagues at the University of Regensburg in Germany reported results from 146 of these patients, who were tracked for an average of nearly 2 years. Blana's team reported in the February 2004 *Urology* that 87 percent of the patients remained free of their cancer. In studies of traditional prostate cancer therapies, up to 95 percent of men with early-stage cancer remain cancerfree at least 5 years after treatment.

At Hachioji Hospital in Tokyo, Toyooki Uchida and his colleagues have treated more than 200 men since 1999.

Overall, 81 percent of the men remained free of disease 1 year after the procedure, and 77 percent had no disease after 5 years, Uchida reported at a meeting of the International Society for Therapeutic Ultrasound in Boston last October.

But more evidence is needed to prove that HIFU rids men of cancer as effectively as established therapies do, says urologist Peter Scardino of Memorial Sloan-Kettering Cancer Center in New York City.

Other researchers are now testing HIFU in patients with terminal liver or brain cancer or patients in whom tumors from other organs have spread to bone. These trials are intended to relieve pain.

JUST WARMING UP In addition to scoring direct hits against cancer, HIFU may provide assists when used in combination with established drugs. Researchers at the National Institutes of Health's Clinical Center in Bethesda, Md., showed at last year's radiology meeting that HIFU can boost the amount of a chemotherapy drug that reaches a tumor. Sergio Dromi and his colleagues injected skin tumor-carrying mice with microscopic envelopes of fat, called liposomes, that contained the anticancer drug doxorubicin. Liposomes carry drugs and other substances into cells.

In some mice, the researchers then used a HIFU machine to deliver intermittent pulses of ultrasound energy to each tumor, elevating its temperature to 42°C and breaking down the liposomes. Examination of the tumors revealed that three times as much doxorubicin reached the target in the HIFU-treated mice as in the other mice.

Other researchers are pursuing HIFU as a method for cauterizing hemorrhaging internal wounds (*SN: 1/6/01, p. 12*) and breaking up blood clots and kidney stones (*SN: 11/26/05, p. 346*).

Suarez, the urologist who treated Reinwald in Santiago, anticipates that HIFU may treat pancreatic and kidney cancer, fix heart arrhythmias, and even improve liposuction.

Use of HIFU for cancer could dramatically reduce health care costs, argues Suarez. It requires little or no hospitalization and less recovery time than alternative treatments do. Because HIFU is associated with a low rate of permanent complications, it also decreases the cost of treating those side effects.

"I'm treating about 20 patients a month [with HIFU]," Suarez says. "We are concentrating on prostate cancer right now. There's a sense of urgency—it is the most common cancer in men." ■

