In From the Cold: Cryotherapy Gets a Second Look

Is cryotherapy an innovative alternative in cancer treatment — or an unfulfilled promise? Individual interest in cryotherapy by doctors treating cancers of the prostate, liver, and breast, to name a few, is generating preliminary clinical trials and sparking debate about the role of this procedure, which is less invasive than surgery.

Cryotherapy is a standard procedure for some cancers. Targeting external tumors, doctors use a spray or swab to apply liquid nitrogen directly to cancer cells to kill them. Dermatologists have long been freezing early stage basal and squamous cell carcinomas. For at least 2 decades, gynecologists also have used cryotherapy to fight cervical dysplasia. And in recent years, awareness of human papillomavirus — implicated in more than 90% of cervical cancer — has prompted physicians to search more vigorously for early signs of the neoplastic changes that precede such cancer. Cryotherapy offers success rates in treating women with abnormal cervical cells similar to those of laser ablation or excision, loop electrosurgery, and cold knife conization.

Against more internal tumors, a doctor uses ultrasound images to guide liquid nitrogen-filled cryoprobes toward clusters of cancer cells. The technique often is less invasive and less costly than surgery. In some cases, cryotherapy may treat inoperable cancers. The major disadvantage is uncertainty over cryotherapy’s ability to destroy all cancerous tissue — for good — while keeping nearby healthy cells intact.

Better Specificity

In the 1960s, physicians first aimed cryoprobes at prostate cancer. But doctors often inadvertently froze surrounding healthy tissue as well, damaging the urethra or creating fistulas between the urethra and rectum. Today, some device makers tout improved technology that heats the urethra during cryotherapy, protecting it while prostate cells freeze. This specificity has prompted some urologists to give cryotherapy a second look, said Michael Manyak, M.D., chairman of urology at George Washington University, Washington D.C., and head of the American Urological Association’s technology assessment council.

“Quite clearly, cryotherapy does kill cells, and it could be used to kill prostate cancer,” Manyak said. “When you look at the data, there is an acceptable rate of [procedural] complications — rectal perforations only occur 1% of the time, and you can often predict which patients are at risk.”

Since 1990, more than 5,000 cryotherapy procedures have been performed on prostate cancer in patients in the United States. It is unclear whether this small wave of interest will rise or fall. Together, Manyak and NCI senior investigator Richard Kaplan, M.D., hope to recruit urologists to begin a clinical trial of cryotherapy against prostate cancer. But they acknowledge that urologists are polarized about the technique’s potential efficacy. One problem is that prostate cancers are usually multi-focal: In these cases, cryosurgery is likely impractical. The technique always causes impotence and inconvenience, so some doctors think cryotherapy is undesirable.

“I don’t believe today that cryotherapy has a viable place in the treatment of prostate cancer, when you consider the alternatives,” said Peter Scardino, M.D., chairman of urology at Baylor College of Medicine, Houston.

“You get a higher complication rate than from surgery and a lower cure rate than radiotherapy. I think the enthusiasm for cryotherapy will gradually translate into enthusiasm for brachytherapy [radiation from close sources — implants, etc.]”

Metastatic Mechanics

Cryotherapy may prove more useful against liver cancer, where the goal is to kill the tumor and only a narrow rim of surrounding tissue, sparing more of the liver than possible during standard surgery. Because the liver is a large, solid organ, it provides a greater — and more easily targeted — margin of tissue than does the prostate — thus decreasing the risk of accidentally freezing healthy cells along with cancerous ones.

In particular, physicians hope to use cryotherapy to treat liver metastasis, particularly from colorectal cancer. Up
to 70% of terminally ill colon cancer patients develop liver metastases. These patients often have liver lesions that are too numerous or too widely distributed for traditional surgical resection. Others are at risk from the operation. For them, cryotherapy is viewed as a new, potentially safer alternative to chemotherapy or as an addition to surgery.

As with the prostate, interest in liver cryotherapy arose at the local level, with doctors reporting varying success rates. At New England Deaconess Hospital, Boston, and Mt. Sinai Hospital, New York, for example, overall survival rates for ultrasound-guided cryoablation of liver tumors that have metastasized from the colon hover above 60%. Complication rates are reportedly low, with operative mortality less than 3%. Up to 2 years later, 25% to 50% of patients remain free of disease.

Major Trial

Intrigued by these cases, the Eastern Cooperative Oncology Group has just launched the first major, multi-institution prospective trial studying cryotherapy as a treatment for metastases found in the liver. “We are cautiously optimistic,” said principal investigator James Peacock, M.D., at the University of Rochester (N.Y.) Cancer Center. “A lot of hospitals and patients have an interest in [cryotherapy]. It is still a strategy that remains to be proven, however.”

The ECOG trial begins with doctors treating 15 colon cancer patients who have liver metastases with ultrasound-guided cryoablation, and then following patient progress with regular computerized tomography scans. If at least nine or 84% of the patients are disease-free at 3 months, ECOG plans to add 27 more people. The researchers hope to complete this two-stage design with at least 17 patients who have disease-free livers at 12 months after cryotherapy. “Our goal is to give surgeons another tool that enables them to treat more patients,” said Peacock.

Like the liver, the breast provides a larger treatment area surrounded by non-critical muscle and skin. Since 1968, more than 60 patients, often with incurable breast cancer, have received cryotherapy worldwide.

Last year, Edgar Staren, M.D., Ph.D., an associate professor of surgery at Rush Medical College, Chicago, and colleagues made news when they announced that they had treated a breast cancer patient with the technique. At the time, the patient had a multifocal tumor. The cancer has recurred in another part of her breast, though not in the area treated.

That case built upon years of animal research in which Staren’s group studied...
breast tumors in mice, rats, sheep, and dogs. Rodent models showed that cryotherapy could, in fact, destroy cancer cells with limited harm to nearby healthy tissue. Once researchers knew cryotherapy worked in small animals, they tried the technique on sheep and dogs. Staren and colleagues found their ultrasound-monitored cryotherapy could accurately treat and track tumor tissue.

Now, Staren and colleagues at three other institutions hope to try cryotherapy against breast cancer in a multi-institution trial. Candidate patients will have small, localized cancers detected by mammograms. “I think surgeons look at this as the logical extension to what they’re already doing to decrease the invasiveness of breast care,” said Staren.

Breast cryotherapy clinical trials have become practical only recently, he added. A clinical trial requires patients to undergo cryotherapy, wait 4 to 7 days, and then undergo an excision to remove the treated tissue for histological studies to ensure that all the cancer cells have been killed. Because doctors can use newer needle biopsy techniques to remove cryotherapy-treated tissue in the office, instead of surgical biopsies in the hospital, trials are now possible.

An Open Mind

Cryotherapy proponents ask doctors to be patient as the technique evolves. Staren notes that until 1979, radical mastectomy was still the norm in breast cancer treatment. And only 7 years ago a National Institutes of Health consensus panel endorsed lumpectomy over modified mastectomy for some cases. “This technique is a groundbreaking idea, and it’s something people should keep an open mind about,” said Manyak.

— Kathryn S. Brown

Organ Transplants Carry a Rare Risk of Hidden Cancers

In 1991, a 42-year-old woman from Northern California was the donor of multiple organs after suffering a fatal brain hemorrhage in the shower. Her kidneys, heart, liver, corneas, bone marrow and skin were all harvested for transplantation. Within a year at least four people, and possibly more than a dozen, died of metastatic melanoma — contracted from the undiagnosed melanoma she harbored within her body.

Cancer in transplant patients is not uncommon. The immunosuppression patients receive to prevent the rejection of the transplanted organ leaves them more vulnerable to cancers and to various infectious agents. Overall, there is a threefold to fourfold increased incidence of cancer in transplant recipients compared with age-matched controls in the general population, according to data from the Cincinnati Transplant Tumor Registry.

But the transplantation of a tumor from donor to patient is exceedingly rare. Of more than 250,000 organ transplants over the last 30 years, less than 100 patients have developed donor-related tumors according to a review article in the August 1997 issue of Digestive Diseases and Sciences.

Last year, in the Journal of the American Medical Association, Evan Loh, M.D., of the University of Pennsylvania School of Medicine, Philadelphia, described an orthotopic heart transplantation in which prostate cancer from the donor was transmitted to the patient. A prostate cancer cell somehow lodged itself, undetected, in the transplanted heart and eventually metastasized to the bones in the ribcage of the patient.

In an interview, Loh said that the transplant priorities were to blame. Collecting all useable organs for transplant is time consuming and not all organs are equally sturdy. While organs that do not last long, such as the heart, are harvested and used as quickly as possible, longer lasting organs are saved for later.

“The kidney can stay out of the body for 50 hours,” Loh said, “so by the time the final dissection is done, you’ve already taken the heart.” Each organ to be transplanted undergoes visual inspection for cancerous tissue. In this case, prostate cancer was found in the donor, but only when the kidneys were being prepared for removal, and the heart was already in the process of being transplanted into the patient. Nothing else from the donor was used, but Loh’s team elected to complete the heart transplant. The patient was diagnosed with metastatic prostate cancer 10 months later.

Loh said he was surprised that the cancer was transplanted. It’s such a rarity that he hadn’t expected any problems. In addition, the heart had shown no sign of cancer when inspected visually. But as the upper age at which donors are accepted increases, he wonders if hidden prostate cancers might become a more serious issue in the future.

Judgment calls with limited time are the norm in transplantation, according to Loh. “It’s mostly the procuring surgeon’s call,” Loh said. “Without a fast screen, especially in a case involving a quick