

## Hyperthermia: Using Heat to Treat Cancer

Among the many cancer treatments currently being studied in clinical trials is a technique called hyperthermia. According to the National Cancer Institute (NCI), hyperthermia is a cancer treatment that exposes skin or tissue a group or layer of cells that work together to perform a specific function. to high temperatures of up to 113°F in a highly controlled or directed manner, and is primarily used in conjunction with other cancer treatments, such as radiation Energy released in the form of particles or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, and medical x-rays. or chemotherapy Treatment with drugs that kill cancer cells. . When the body cells are exposed to such high levels of heat, changes occur within the cells that can either destroy them or make them more susceptible to the other cancer-killing agents being used to treat your cancer.

There are three main types of hyperthermia treatment: local, regional In oncology, describes the body area right around a tumor. , and whole-body. In local hyperthermia, heat is applied to a designated or small area, such as the site of a tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancerous), or malignant (cancerous). Also called neoplasm. . According to the NCI, there are three approaches to local hyperthermia, depending on where the tumor is located:

- External - These approaches are used to treat tumors that are in or just below the skin, and involves high-energy waves aimed at the tumor from an external machine. "Usually this is done using microwave or ultrasound A procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues called a sonogram. Also called ultrasonography. applicators," says Mark W. Dewhirst, DVM, PhD, Gustavo S. Montana professor of radiation oncology The study of cancer. and professor of pathology and biomedical engineering at Duke University Medical Center in Durham, North Carolina. "Both are approved by the FDA for this treatment, when combined with radiotherapy The use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called radiation therapy and irradiation. ."
- Intraluminal or endocavitary - These approaches may be utilized for treating deep tissue tumors or tumors near or within body cavities, and involves a probe inserted into the cavity and the tumor to deliver high-energy waves directly to the tumor. Dr. Dewhirst says these methods are not widely used. "With proper care, though, they are no more dangerous than external applicators," he says. "You cannot say they are more effective than any other method. They are used for tumors that are not heatable with other methods. One method that is rather exciting, however, is an ultrasound applicator that is placed within the rectum to heat the prostate A gland in the male reproductive system. The prostate surrounds the part of the urethra (the tube that empties the bladder) just below the bladder, and produces a fluid that forms part of the semen . It is quite sophisticated."
- Interstitial - These approaches treat brain tumors or other tumors deep within the body using an image-guided needle or probe inserted into the tumor to deliver high-temperature heat directly to the cancerous tissue. "These methods are also not used extensively," Dr. Dewhirst says. "The invasiveness makes them expensive and rather impractical for modern day hyperthermia." Radiofrequency ablation The use of electrodes to heat and destroy abnormal tissue. (RFA) is a commonly used interstitial hyperthermia treatment, which uses a thin probe inserted into the tumor to deliver high-energy radio waves to deliver heat directly to the cancer site. RFA is most commonly used to treat tumors in the kidney One of a pair of organs in the abdomen. Kidneys remove waste from the blood (as urine), produce erythropoietin (a substance that stimulates red blood cell production), and play a role in blood pressure regulation. , liver A large organ located in

the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. , and lungOne of a pair of organs in the chest that supplies the body with oxygen, and removes carbon dioxide from the body. , and is most often used for tumors that cannot be removed surgically or in patients who are unable to undergo surgery.

Regional hyperthermia involves heating an area of the body, such as a body cavity, organA part of the body that performs a specific function. For example, the heart is an organ. , or limb. Whole-body hyperthermia is being studied in patients with metastatic cancerCancer that has spread from the place in which it started to other parts of the body. as a way to make chemotherapy agents work more effectively. With this technique, body temperatures are raised using methods such as heating blankets or thermal chambers in order to stimulate the body's immunity.

#### Use and Side Effects

Hyperthermia is generally used in conjunction with other cancer treatment, including chemotherapy and radiation. "It has been shown that increased heat has made cancer cells more responsive to radiation," says Theodore L. DeWeese, MD, professor and chairman of the department of radiation oncology and molecular radiation sciences at The Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland. During a course of radiation, which usually involves treatment 5 days a week for several weeks, hyperthermia may be used 3 out of the 5 days each week, and is typically given within an hour before the radiation is delivered.

Careful temperature control is important for optimal effectiveness of this treatment and to minimize damage to surrounding normal tissue. This treatment is most effective when delivered within an exact temperature range and for a certain length or time, depending on the type of tissue being treated. Different tissues have varying sensitivities to heat and can respond differently, and so the temperature and length of exposure must be closely monitored during treatment. For deep-seated tumors, this presents some new challenges. "Attempting to treat such deep tumors is challenging and may increase the risk of side effects," says Dr. DeWeese. There may also be implications on fertility during hyperthermia treatment, particularly if it is used in the pelvic region. Some other side effects can include topical burning, pain, blisters, and discomfort for patients, but these depend on the area being treated and the type of treatment (for example, local vs. whole-body).

Some patients may not be good candidates for hyperthermia, such as those with pacemakers and who have previously undergone extensive radiation therapyThe use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called radiotherapy and irradiation. . Your doctor will be able to discuss this treatment, whether it is right for you, and the possible side effects.

According to Dr. DeWeese, there have been several success stories with hyperthermia in combination with radiation. "One important, recent study was completed in women with cervical cancerCancer that forms in tissues of the cervix (the organ connecting the uterus and vagina). It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests (a procedure in which cells are scraped from the cervix and looked at under a microscope). . The women in the study who received radiation and hyperthermia experienced a nearly doubling of their survival compared to women treated with radiation alone," he adds.

## Measuring Effectiveness

Dr. Dewhirst says the gold standard for measuring success of any therapy is a phase III clinical trial, in which subjects are assigned to either one treatment or another (in other words, either the treatment being investigated or the “control,” or current standard/common treatment) to compare the effectiveness of each. “There have been over a dozen published phase III trials showing that hyperthermia improves treatment outcomeA specific result or effect that can be measured. Examples of outcomes include decreased pain, reduced tumor size, and improvement of disease. when combined with radiotherapy or chemotherapy,” says Dr. Dewhirst. He says diseases in which this has been shown include head and neck cancerCancer that arises in the head or neck region (in the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx [voice box]). , recurrences of breast cancerCancer that forms in tissues of the breast, usually the ducts (tubes that carry milk to the nipple) and lobules (glands that make milk). It occurs in both men and women, although male breast cancer is rare. occurring in the chest wall, locally advanced cervixThe lower, narrow end of the uterus that forms a canal between the uterus and vagina. cancer, esophageal cancerCancer that forms in tissues lining the esophagus (the muscular tube through which food passes from the throat to the stomach). Two types of esophageal cancer are squamous cell carcinoma (cancer that begins in flat cells lining the esophagus) and adenocarcinoma (cancer that begins in cells that make and release mucus and other fluids). , bladder cancerCancer that forms in tissues of the bladder (the organ that stores urine). Most bladder cancers are transitional cell carcinomas (cancer that begins in cells that normally make up the inner lining of the bladder). Other types include squamous cell carcinoma (cancer that begins in thin, flat cells) and adenocarcinoma (cancer that begins in cells that make and release mucus and other fluids). The cells that form squamous cell carcinoma and adenocarcinoma develop in the inner lining of the bladder as a result of chronic irritation and inflammation. , primary brain tumors, melanomaA form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but can also begin in other pigmented tissues, such as in the eye or in the intestines. , and soft tissue sarcomaA cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. . All of these trials used a control arm involving radiotherapy or chemotherapy alone versus an investigation arm involving that same treatment along with hyperthermia, Dewhirst says.

## The Future of Hyperthermia

Dr. DeWeese says one of the most exciting prospects for hyperthermia in the future relates to the development of targeted, iron-oxide nanoparticles. He explained that these very tiny particles contain iron and are coated with antibodies that help direct the particles specifically to tumor cells after they are injected. “Once in the tumor, the particles can be heated by placing the patient into a magnetic field,” says Dr. DeWeese. “This exciting evolution holds the promise of more specific heating of tumor cells anywhere in the body while also minimizing the risk of heating normal cells.”

Several clinical trials are ongoing to increase understanding of how hyperthermia works and how to improve it, to refine how it can be used to enhance the effectiveness of other cancer therapies, and how it can be used to help treat other types of cancer, such as pancreatic and thyroid.