

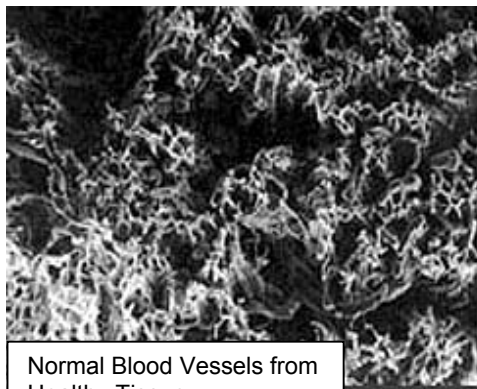


Hyperthermia as a Cancer Therapy

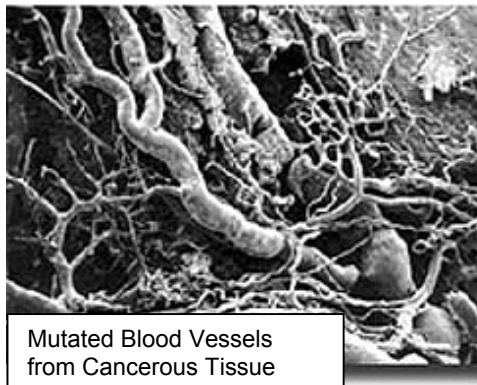
Microwave hyperthermia is a non-ionizing form of radiation therapy that can substantially improve results from cancer treatment. In Phase III clinical trials where hyperthermia was combined with ionizing radiation treatments, hyperthermia improved 2-year local control of melanoma from 28% to 46%, complete response for recurrent breast cancer from 38% to 60%, 2-year survival for glioblastoma (brain cancer) from 15% to 31% and complete response for advanced cervical cancer from 57% to 83%, as compared to the use of ionizing radiation therapy alone.

Vulnerability of Cancerous Tumors

Cancerous tumors are growths of mutated cells that often require far more energy to survive than do normal cells. As cancer cells multiply unchecked, they can quickly outstrip the capacity of their existing blood vessels to supply enough oxygen and nutrients to support them. In response, malignant tumors stimulate growth of additional blood vessels. However, these new blood vessels are mutated chaotic structures, as compared to blood vessels of normal tissues—of odd sizes, with loops and even blind ends. Because of this irregular blood vessel structure and rapid tumor growth, there are often large areas in tumors where the blood supply is deficient.



Normal Blood Vessels from Healthy Tissue



Mutated Blood Vessels from Cancerous Tissue

Cancerous tumors that do not have an adequate blood supply become oxygen starved (hypoxic) because blood is the source of oxygen delivery for cells. They also become acidic because hypoxic tumors cannot adequately expel waste through the blood. These tumors can even experience wide fluctuations in blood flow as their unstable blood vessels periodically collapse, making them acutely oxygen deficient for periods of time. Oxygen starved cancer cells are difficult to kill with ionizing radiation (which creates oxygen radicals that attack tumor DNA) or chemotherapy (where blood transport is required to deliver the drug). Destroying blood/oxygen depleted cancer is a very high priority in cancer therapy because hypoxic cancer cells are especially dangerous, prone to metastasize and spread the cancer to other parts of the body.

How Hyperthermia Kills Cancer Cells

Hyperthermia destroys cancer cells by raising the tumor temperature to a “high fever” range, similar to the way the body uses fever naturally when combating other forms of disease. Because the body’s means of dissipating heat is through cooling from blood circulation, sluggish or irregular blood flow leaves cancerous tumors vulnerable to destruction at elevated temperatures that are safe for surrounding healthy tissues with normal, efficient blood cooling systems.

Scientists attribute the destruction of cancer cells at hyperthermic temperatures to damage in the plasma membrane, the cytoskeleton and the cell nucleus. Cancer cells are vulnerable to hyperthermia therapy particularly due to their high acidity caused by the inability to properly expel waste created by anaerobic metabolism. Hyperthermia attacks acidic cells, disrupting the stability of cellular proteins and killing them.

How Hyperthermia Increases the Effectiveness of Ionizing Radiation

Hyperthermic temperatures increase blood circulation in tumors as the body’s response to the stimulus of heat. This increased presence of oxygen-bearing blood in tumor tissues is critical for making ionizing radiation more effective. Ionizing radiation destroys tumor cells substantially through the formation of oxygen radicals that attack tumor cell DNA. Oxygen-starved cells are three-times more resistant to ionizing radiation than are normal cells. It has been demonstrated that low oxygen levels in human tumors (hypoxia) is directly linked to failure in achieving local tumor control through ionizing radiation, and the degree of oxygen deficiency in cancerous tumors is a key predictor of the efficacy of ionizing radiation therapy.

While oxygen radicals attack cancer cell DNA, hyperthermia acts further to create an accumulation of proteins in the cell nucleus that bind to the nuclear matrix, disrupting the repair of radiation-induced DNA damage. Hyperthermia provides additional potentiation of ionizing radiation due to the growth cycle of cancer cells. During the S-phase of cell division when cancer cells are aggressively resistant to the effects of ionizing radiation, they are susceptible to the destructive effects of hyperthermia.

The conditions that enhance the effects of hyperthermia are typically those that reduce the effects of ionizing radiation. Low blood flow tumor tissues resistant to ionizing radiation are sensitive to hyperthermia, while tumor tissues with high blood flow are sensitive to ionizing radiation. This highly complementary interaction is compelling reason for combining hyperthermia and ionizing radiation (thermoradiotherapy). *In vivo* studies have demonstrated that the effects of ionizing radiation can be enhanced by a factor between 1.2 and 5, making hyperthermia the most potent sensitizer to ionizing radiation therapy known.

How Hyperthermia Increases the Effectiveness of Chemotherapy

For chemotherapy drugs that depend on blood transport for delivery, hyperthermia used in combination with chemotherapy (thermochemotherapy) enhances blood flow in tumor tissues, increasing the uptake of chemotherapy drugs in tumor membranes. Hyperthermia also induces disassembly of the cytoskeleton, which enlarges the tumor pores for easier drug entry. Once delivered, hyperthermic temperatures can be used as a drug activator, accelerating chemical reactions through heat and drawing essential oxygen molecules to tumor tissue for chemical reaction with the drug. Reviews have been given of the interactions of hyperthermia with a wide range of chemotherapy drugs including doxorubicin, mitomycin C, mitoxantrone, bleomycin, cisplatin, nitrosoureas and cyclophosphamide. Hyperthermia has demonstrated the ability to enhance drug toxicity in cells rendered resistant to many drugs used in chemotherapy.

Hyperthermia is proving a role as a valuable companion therapy when chemotherapy drugs are injected into the blood in encapsulations called "liposomes". Research has shown that when a liposome-encapsulated drug is used in combination with hyperthermia therapy directed on a tumor, drug penetration can dramatically increase. Research is also being conducted on heat-activated liposomes that use hyperthermic temperatures as the release mechanism for the encapsulated drug when they reach the tumor.

Hyperthermia can be employed synergistically with chemotherapy in strategies to treat bulky tumors. The cores and other regions of these tumors are often difficult to penetrate with drugs because of low blood flow in up to a third of the mass of the tumor. In addition, chemotherapeutic drugs act best on rapidly dividing cells.

As blood starved cancer cells are growth retarded, chemotherapy has limited efficacy against them. Hyperthermia is able to attack cancer cells in blood-deficient regions of the tumor while the drug permeates tissues with higher blood flow nearer the surface, providing potentiation of drug uptake.

Hyperthermia and Surgery

Tumors tend to shrink (often dramatically) when treated with hyperthermia due to the collapse of dead cancer cells. This can make tumor removal through surgery easier or even possible. Hyperthermia has particular preoperative value when tumor removal is dangerous or not possible because of proximity to vulnerable adjacent tissue. Additional benefits of hyperthermia include the potential for reduced disfigurement resulting from surgical removal of tumors of the head and neck or other conspicuous parts of the body by shrinking the tumor prior to surgery.

Hyperthermia and Biological Therapies

Gene therapy research is showing hyperthermia to be an activator to turn on new biological therapies, speeding gene production by thousands of times (heat mediated gene therapy). Hyperthermia plays an essential role in the development of anti-tumor vaccines that are based on heat shock proteins. Research is showing hyperthermia to be an angiogenesis inhibitor, preventing cancer from inducing growth of new blood vessels to expand its blood supply. Hyperthermia has further demonstrated use as a companion therapy for drug angiogenesis inhibitors, used in the final destruction of depleted cancer cells that survive blood starved conditions.

Hyperthermia and Quality of Life

A recent study by the National Academy of Sciences has pointed out the shortcomings of the single-minded search for cancer cure while ignoring existing patients who need treatment for pain and other conditions associated with cancer. A substantial improvement in both palliation and durability of palliation has been observed when hyperthermia is added to ionizing radiation treatments. Some scientists have noted that hyperthermia stimulates the immune system, assisting patients in recovery from toxic cancer therapies such as chemotherapy and ionizing radiation. Even in situations where there is no hope for survival, hyperthermia may provide benefit through alleviation of such effects as bleeding, pain and infection.

Position of the Research and the FDA

In January 2001 an article entitled "Hyperthermia in Oncology" appeared in the *International Journal of Hyperthermia*, offering an overview of hyperthermia clinical

trials performed during the last decade and a half on more than 2,200 patients with cancer. Doctors M. H. Falk and R. D. Issels, noted leaders in hyperthermia research, concluded that, “especially in well defined clinical situations in breast cancer, melanoma, head and neck tumors, cervix cancer and glioblastoma, the addition of hyperthermia to radiotherapy [ionizing radiation] significantly improves response and survival, and thus should be considered presently proven therapy.” (See Vol. 17, No. 1, 1-18.)

BSD Medical Corporation has received FDA approval for hyperthermia treatment for use alone or in conjunction with ionizing radiation therapy in the palliative management of solid surface and subsurface malignant tumors; i.e., melanoma, squamous-cell or basal-cell carcinoma, adenocarcinoma, or sarcoma, that are progressive or recurrent despite conventional therapy.

Accumulated Findings from the Research

The National Cancer Institute recognizes hyperthermia as a therapy for treating cancer and has contributed tens of millions of dollars to the research, development and advancement of hyperthermia therapy. European contributors have been no less generous. The German Cancer Aid Foundation has given hyperthermia a priority status as one of the few new weapons against cancer that demonstrates efficacy. The German Federal Research Council has also been an important benefactor. The Dutch Health Insurance Council funded a landmark study of the use of hyperthermia in treating certain pelvic cancers. The European Organization for Research and Treatment of Cancer (EORTC) has provided quality control for many millions of dollars contributed to hyperthermia research throughout European nations. Much of the hyperthermia equipment used in this worldwide research effort was developed and manufactured by BSD Medical Corporation.

Research sites using BSD Medical Corporation’s high-end technology for delivering hyperthermia include Duke University Medical Center, Northwestern University Medical School, University of Southern California, Centennial Medical Center, Daniel den Hoed Cancer Center of the Academisch Ziekenhuis (Rotterdam, The Netherlands), Haukeland University Hospital (Bergen, Norway), Dusseldorf University Medical School, Tübingen University Medical School, Essen University Hospital, Charité Medical School of Humboldt University (Berlin), Luebeck University Medical School, Munich University Medical School Grosshadern, Interne Klinik Argirov of the Munich Comprehensive Cancer Center (all of Germany), University of Verona Medical Center (Italy), Graz University Medical School (Austria) and Kantonsspital Aarau (Switzerland).

The accumulated data and experience from many clinical trials has produced the following list of therapeutic benefits for hyperthermia:

- *Improved survival from cancer*
- *Increased local tumor control and duration of local tumor control*
- *Increased remission from cancer*
- *Decreased morbidity from cancer*
- *Direct tumor cell destruction*
- *Improved palliative effect and durability of effect*
- *Improved quality of life*
- *Increased efficacy from other therapies without adding toxicity*
- *Improved tumor oxygenation to enhance ionizing radiation*
- *Destruction of heat-sensitive radiation-resistant cells*
- *Increased tumor response to chemotherapeutic agents*
- *Increased range of size and condition of tumors that can be treated*
- *Increased chemotherapy drug uptake in tumors*
- *Super-additive interactions with chemotherapeutic drugs*
- *Destruction of chemotherapy-resistant cells*
- *Activator for gene therapies*
- *Reduced tumor size, making resection possible and/or less harmful*
- *Reduced disfigurement resulting from surgical resection of tumors*
- *Improved functional results from surgery*
- *Increased efficacy from re-irradiation using ionizing techniques*
- *Improved results when used in combination with ionizing radiation and chemotherapy (thermoradiochemotherapy)*

Results from Major Studies

Over the past fifteen years there have been 33 published clinical trials (17 Phase I or II and 16 Phase III) on the effects of hyperthermia combined with ionizing radiation, chemotherapy or both. The following published studies completed at notable research centers in North America and Europe are among the most significant:

In 1993 the *International Journal of Radiation Oncology, Biology, Physics* reported the results of a 41 patient (44 node) Phase III clinical trial involving inoperable Stage IV head and neck cancer conducted by Valdagni and Amichelli at the Institute of Science and Technology at Ricerca, Trento, Italy. The study concluded that hyperthermia added to ionizing radiation improved complete response from 41% to 83%, local relapse-free survival from 24% to 68% and overall survival at 5 years from 0% to 53%, as compared to ionizing radiation treatments alone. (See Vol. 28, pp. 163-169.)

In 1996 the *International Journal of Hyperthermia* reported the results of Phase III clinical trials on 128 tumors involving recurrent or metastatic malignant melanoma as conducted by Overgaard, Gonzalez Gonzalez, Hulshof, Arcangeli, Dahl, Mella and Bentzen, and performed at the Danish Cancer Society Aarhus University Hospital, Denmark, Academisch Medisch Centrum, Amsterdam, The Netherlands, G. Porfiri Oncology Centre, Latina, Italy and the Haukeland Hospital, Bergen, Norway. The study concluded that the addition of hyperthermia to ionizing radiation increased the complete response rate of recurrent malignant melanoma lesions from 35% to 62%, and local relapse-free survival at five years from 28% to 46%, as compared to ionizing radiation treatments alone. (See Vol. 12, No. 1, 3-20.)

In 1996 the *International Journal of Radiation Oncology, Biology, Physics* reported the results of a 306 patient Phase III clinical trial involving superficial localized breast cancer conducted by Vernon, Hand, Field, Machin, Whaley, van der Zee, van Putten, van Rhoon, van Dijk and Gonzalez Gonzalez at Hammersmith Hospital, London and MRC Cancer Trials Officer, Cambridge, United Kingdom, Daniel den Hoed Cancer Center, Rotterdam and Academic Medical Center, Amsterdam, The Netherlands and Prince Margaret Hospital, University of Toronto, Canada. The study concluded that the addition of hyperthermia to ionizing radiation increased complete response from 41% to 59% and local relapse-free survival from 30% to 50%. (See Vol. 35, No. 4, pp. 731-744.)

In 1996 the International Journal of the American Cancer Society, *CANCER*, reported the results of a 23 patient clinical trial involving carcinoma of the head and neck region, carcinoma of the breast and malignant melanoma, conducted by Lee, Mayer and Hallinan of Johns Hopkins Hospital. The study produced complete response in 89% of patients and partial response in 11% of patients, with a two-year actuarial local control rate of 74% using interstitial hyperthermia in combination with radioactive seeds (brachytherapy). The study concluded that "outpatient interstitial thermoradiotherapy is convenient, safe, and efficacious for treating human neoplasms". (See 77/11, pp. 2363-2370.)

In 1998 the *International Journal of Radiation Oncology, Biology, Physics* reported the results of a 112 patient Phase III clinical trial involving glioblastoma multiforme (brain cancer) conducted by Sneed, Stauffer, McDermott, Diederich, Lamborn, Prados, Chang, Weaver,

Spry, Malec, Lamb, Voss, Davis, Wara, Larson, Phillips and Gutin at the University of California, San Francisco. The study showed a more than double two-year survival rate using brachytherapy plus hyperthermia as compared to brachytherapy alone. (See Vol. 40, No. 2, pp. 287-295.)

In 1999 the *International Journal of Radiation Oncology, Biology, Physics* reported the results of a 97 patient Phase III clinical trial involving high-grade soft tissue sarcomas conducted by Prosnitz, Maguire, Anderson, Scully, Harrelson, Jones, Dewhurst, Samulski, Powers, Rosner, Dodge, Layfield, Clough and Brizel at Duke University Medical Center, Durham, North Carolina. This study showed excellent local control of extremity lesions (95% control) when hyperthermia was combined with radiation. (German clinical trials have also reported that hyperthermia enhances the effectiveness of certain chemotherapy drugs, even in drug-resistant cells, when treating locally advanced sarcomas.) (See Vol. 45, No. 4, pp. 941-949.)

In 2000 *THE LANCET* reported the results of a 358 patient Phase III clinical trial involving locally advanced pelvic tumors that was conducted by van der Zee, Gonzalez Gonzalez, van Rhoon, Dijk, van Putten and Hart and the Dutch Hyperthermia Group at University Hospital-Daniel den Hoed Cancer Center, Rotterdam and Academic Medical Center, Amsterdam, The Netherlands. The study reported that hyperthermia in combination with ionizing radiation improved complete response rates for bladder cancer from 51% to 73%, complete response rates for advanced cervical cancer from 57% to 83%, and overall three-year survival from 27% to 51%. (See Vol. 355, pp. 1119-1125.)

This document has been prepared by BSD Medical Corporation for informational purposes. Although there is much to support the use of hyperthermia for cancer therapy, the viability of any therapy can change with continued discoveries and new treatments. Statements contained in this document that are not historical facts are forward looking statements, as that item is defined in the Private Securities Reform Act of 1995. Such forward-looking statements are subject to risks and uncertainties (detailed in the Company's filings with the Securities and Exchange Commission) that could cause actual results to differ materially from estimated results.

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