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A REVIEW ON POTENTIAL BENEFITS OF HYPERTHERMIA IN THE TREATMENT OF CANCER

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ABSTRACT

Hyperthermia treatment is exposing the body to supra normal temperature which is elevated to kill the cancerous cells without damaging the healthy tissues. Hyperthermia is a cancer treatment technique in which the temperature of the affected part of the body is slightly raised (41.5 to 43^0C / 104 -113 ^{0}F) to damage and kill cancer cells or to make cancer cells more susceptible to radiotherapy or chemotherapy. Hyperthermia could be considered as the forth pillar for the treatment of cancer in addition to radiotherapy, chemotherapy and surgery. Treatment strategy involving hyperthermia combined with radiotherapy/ biotherapy/ chemotherapy/ surgical intervention results in higher response rates, improved tumor control, better palliative effects and better overall survival rates.

INTRODUCTION

The knowledge about heat treatment of tumors is as old as the written text in medicine. Thus, the Edwin Smith Surgical papyrus, which was probably the first medical textbook dating back more than 5000 years, contains a description of a patient with a tumor in the breast treated with Hyperthermia [1]. Though hyperthermia therapy is considered for wide range of illnesses in ancient days, e.g Sand bathing in hot sun for heart diseases. Its complimentary and augmentation efficacy in malignant conditions are highly considered during harsh chemotherapy. In the last decades of the nineteenth century, Hyperthermia underwent a rebirth triggered by observations that patients with high fever due to erysipelas (also known as holy fire or Saint Anthony's fire in which patients suffer with very high fevers) in some cases demonstrated spontaneous regression of tumors. This led the New York surgeon William B. Coley to develop his "Mixed Bacterial Toxin" and thereby he became the father of both the modern use of hyperthermia and the non specific immunotherapy for the treatment of cancer. At the same time with the Coley's interest, some others also performed the application of hyperthermia and observed that rise in temperature < 45ºC could revert the tumors [2,3]. Moving forward, this treatment principle was established in the beginning of this century. Hyperthermia is the elevation of temperature inside a tumor from 41.5 to 43ºC without exceeding the limits of tolerance of neighboring normal tissues. This kills many cancer cells since many of them are stressed cells for reasons such as poorly structured/perfused blood vessels which restricts amount of oxygen and nutrients available to them. Heat also helps to expose the tumor antigens (a substance that induces an immune response) so an effective immune response can be achieved by the immune system of the

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body [4,5].

Effects of Hyperthermia on Tumor Blood Flow (TBF) and Normal Blood Circulation

The human body naturally uses heat as a essential mechanism to fight disease. For example viruses and bacteria spread very rapidly in the human body at normal temperature 37ºC. The body promptly defends itself by increasing its temperature several degrees to slow down the rapid multiplication of such disease causing agents. This phenomenon, commonly known as fever, gives the body an advantage while fighting the infection.

Solid tumors tend to have a more acidic and hypoxic microenvironment than normal tissue. This hostile microenvironment results from a disparity between oxygen supply and demand of the tumor tissue [5]. Cancer cells grow until oxygen demand exceeds supply and the distance from host vessels is lower than 100-200 µm [3]. Although cancer cells are destroyed by hyperthermia alone, many factors, including the cell type and blood perfusion, influence its success. In fact, it has been shown experimentally and theoretically that heat transferred away from a tissue depends upon the rate and the volume of blood flowing through that tissue (perfusion) [6,7]. Tumor cells in a hypoxic environment are 2 to 3 times more resistant to radiation damage than those in a normal oxygen environment [2].

The relationship between temperature rise and perfusion is inversely correlated: as the perfusion rate decreases, the tumor temperature increases [8]. The gap in temperature obtainable between normal and tumor tissue is due to the differences in conduction and convection characteristics between the two tissues [11]. Tumor blood flow and distribution are different from normal tissue and show regional variations in the same tumor itself [9].Tumor blood flow appears to be inferior to that of normal tissue and to have a decreased adaptability to metabolic demands and physical stress (heat) [10]. The vasodilatation (expansion of blood vessel) that happens after heat application to normal tissues is not present at the same extent in tumor vasculature [11-14].

This determines a decreased convection and permits to entrap heat in the tumor area, rising the temperature in that target area [13, 14]. In fact, different authors heating deep seated human tumors by radiofrequency (13.56 MHz) therapy, have reported that tumor temperature was higher than that of surrounding normal tissue [14,15]. Different authors studied RBC velocity and vessel lumen diameter in mature granulation tissue and in neoplastic tissue (VX2 carcinoma). They found and confirmed the above-mentioned observations, but noted that stasis (stoppage of the normal blood flow) occurred in normal and tumor tissue both. The difference in stasis was dependent on temperature [13,14,16]. In fact, the stasis in normal tissue occurred later and at higher temperature (47°C) whereas stasis in tumor tissue was reached before and at a lower temperature (41°C) [14]. The recovery kinetics of tumor blood flow after heating was temperature dependent, i.e., blood stasis occurred in the range 3-5 hr after heating, remaining low for 24 hr and partially recovering after 48 hr [11]. Aside the vasodilatation a complexity of other events follow heat application. They are different biochemical and microcirculatory changes, such as: acidosis, RBC stiffening and aggregation, degenerative changes of endothelium, increased vascular permeability, platelet aggregation, leukocyte sticking and intravascular clotting [14,15]. These phenomena worsen the tumor microenvironment further and explain why neoplastic cells are damaged more easily by temperature (42-45°C) than normal cells [7]. Thus vascular modulating effect during hyperthermia induction, the pathological state plays vital role in achieving the desired therapeutic efficacy, absolutely without medicines.

Heating Techniques for Hyperthermia

For every form of hyperthermia to be accurately delivered and evaluated in clinical trials, it is essential to achieve most favorable quality control of heat delivery and temperature monitoring in patients. The choice of hyperthermia used depends upon the location and size of the tumor in the body. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumor and surrounding tissues is monitored throughout the hyperthermia procedure. Hyperthermia can be differentiated into three divisions: the local, regional and whole-body hyperthermia.

Local Hyperthermia

In this method heat is supplied to a small area, such as tumor, using various techniques that deliver energy to heat the tumor. Different types of energy may be used to apply heat, including microwave, radiofrequency and, ultrasound. Depending on the tumor location. There are several techniques like External, Intraluminal or endocavitary and interstitial to achieve local hyperthermia.

External Technique

This technique is used to treat tumor which are in or just below the skin. External applicators are positioned around or near the appropriate region, and energy is focused on the tumor to raise its temperature. Fig 5. Shows local hyperthermia technique.

Intraluminal/Endocavitary Technique

This technique is used to treat tumors within or near body cavities, such as the esophagus or rectum. Probes are placed inside the cavity and inserted into the tumor to deliver energy and heat the area directly.

Interstitial Technique

This technique is used to treat tumor deep within the body, such as brain tumors. This technique allows the tumor to be heated to higher temperatures than external techniques. Under anesthesia, probes or needles are inserted into the tumor. Imaging techniques such as ultrasound, may be used to make sure the probe is properly positioned within the tumor. The heat source is then inserted into the probe. Radiofrequency ablation (RFA) is a type of interstitial hyperthermia that uses radio waves to heat and kill cancer cells.

Regional Hyperthermia

Commonly three techniques are used for regional hyperthermia to heat large area of tissue, such as body cavity, organ or limb.

Deep Tissue Technique

This technique is used to treat cancer within the body, such as cervical or bladder cancer. External applicators are placed around the body cavity or organ to be treated. Microwave or radiofrequency energy is focused on the area to increase its temperature.

Regional Perfusion Technique

This technique is used to treat the cancer in the arms and legs, such as melanoma, or cancer in some organs such as in the liver or lungs. In this method, some of the patient’s blood is drawn, heated to some desired temperature, and then pumped back (perfused) into the limb or organ. Anticancer drugs are given during this procedure.

Continuous Hyperthermic Peritoneal Perfusion Technique (CHPP)

This technique is used to treat cancers within the peritoneal cavity (the space within the abdomen which contains stomach, intestine and liver), including primary peritoneal mesothelioma (cancer within the lining of the chest, abdomen, or around the heart) and stomach cancer. During surgery, heated anticancer drugs flow from a warming device through the peritoneal cavity. For this treatment, the advantages of chemotherapy are synergistically (combine effect) exploited with the advantage of high local concentration of cytostatic drugs (suppressing of cellular growth and multiplication) with the additive effect of hyperthermia and reduction of therapy resistance through heat [4].

Whole Body Hyperthermia

This hyperthermia is used to treat metastasis cancer. This is a type of a cancer which spreads throughout from its primary location to one or more sites in the body. This hyperthermia can be achieved by several method to raise the body temperature. Temperature range is 39-40ºC in moderate form, and 41.5-42.5ºC in extreme form. [4]. In Russia, a super-extreme form of whole body hyperthermia with temperature range of 43-44ºC is carried out under a certain co- medicine [4]. Fig 6. Shows whole body hyperthermia technique.

Complimentary Effect of Hyperthermia

Hyperthermia alone is damaging to cancerous cells but it is most effective when used in conjunction with radiation therapy or chemotherapy. Research results show that its response rate is excellent when used as combination therapy. Radiation requires oxygen to effectively destroy tumor cells. Hyperthermia causes the dilation of the tumor blood vessels which increases the availability of oxygen. Radiation interacts with oxygen to create chemicals that cause the death of cancer cells. Hyperthermia also disables the tumor cells ability to repair any damage caused by radiation so these cells can die. Chemotherapy treatments markedly benefit from dilation of tumor blood vessels so chemotherapeutic drugs can get to the center of a tumor. Fig 1 and Fig 2 demonstrate the complimentary effects of hyperthermia. Table 2. Showing the benefits of hyperthermia combined with radiotherapy.

Vascular Changes due to Thermal Effects of Hyperthermia in Tumor

At higher temperature one may see a very transient increase in blood flow during the heating period and vascular change soon begins to occur and this will rapidly lead to a decrease in tumor blood flow [27-28].With higher temperature, there is also corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability. This lack of oxygen will also give rise to a decrease in tumor pH level and ultimately lead to cell death [27]. Normal tissues typically show a very different vascular response to heat with flow essentially increasing as the temperature increase [29-30]. Fig 3 and Fig 4 indicate the thermal effect of hyperthermia on tumor and normal tissues.

Thermal Dose

The time in minutes for which the tissue is exposed to suffer biological damage at some particular temperature. Thermal dose is very import in hyperthermia process and required to be measured with complete accuracy [17].

Side Effects of Local Hyperthermia

The possible side effects of hyperthermia depend on the technique being used and the part of the body being treated. Most side effects are short-term, but some can be serious. Local hyperthermia can cause pain at the site, infection, bleeding, blood clots, swelling, burns, blistering, and damage to the skin, muscles, and nerves near the treated area.

Table 1. Methods for Induction of Heat In The Tissue [4]

Method	**Physics**
Heat Exchange	
Thermal conduction	Conduction Equilibrium of Thermal Gradients
Electromagnetic Waves	
Radiofrequency Current	Electron Flow between Atoms Joule Heating
Microwave Radiation	Oscillations of Polar H2O Molecules Dielectric Heating
Laser	Absorption of Light Energy
Ultrasound	
Pressure Waves	Compression –Expansion Forces Mechanical Friction Losses
Alternating Magnetic Field	
Inductive (alternating magnetic field)	Ferromagnetic liquid* (nano particles) or "seeds"

*magnetic liquids (Fe_2O_3/Fe_3O_4), thermo seeds (cobalt/palladium)

Table 2. Randomized Trials Showing Benefits with Hyperthermia HT [26]

Ref.No	**Tumour**	**Treatment**	**Patients (lesions)**	**End Point**	**Effect with HT**	**Effect with-out HT**
25,18	Lymphnodes of head & neck tumors	RT	41 (44)	CR rate 5 yr local control 5 yr survival	83% 69% 53%	41% 24% 0%
19	Melanoma	RT	70 (138)	CR rate 2 yr local control	62% 46%	35% 28%
20	Breat	RT	306	CR rate	59%	41%
21	Rectum	RT, surgery	115	5 yr survival	36%	7%
22	Cervix	RT	64	CR	55%	31%
23	Cervix	RT	40	CR	85%	50%
24	Rectum	RT	14	Response	100%	20%

RT= Radiotherapy, CR= Complete Response

Fig 1. Complete Remission Rates of Patients with Primary Radiated and Recidivated Cervix Carcinoma Comparison of Radio Therapy (RT) with Radio therapy Plus Hyperthermia (HT) [4]

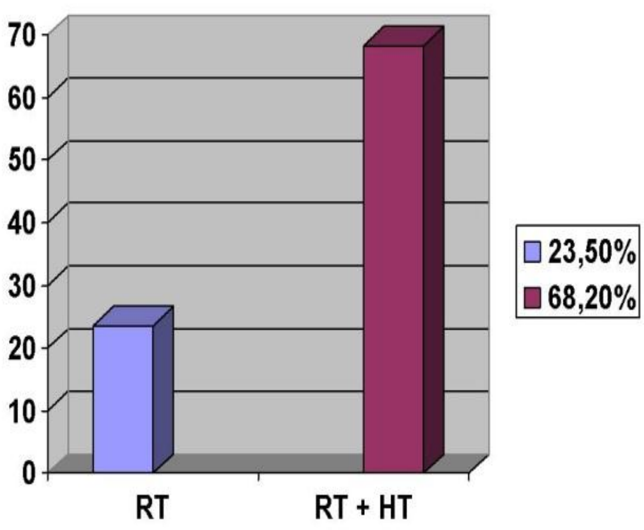


Fig 2. Survival Rates of Patients with Advanced Cervix carcInomas. Comparison of Radio therapy (RT) and of Radio therapy Plus Hyperthermia (HT) [4]

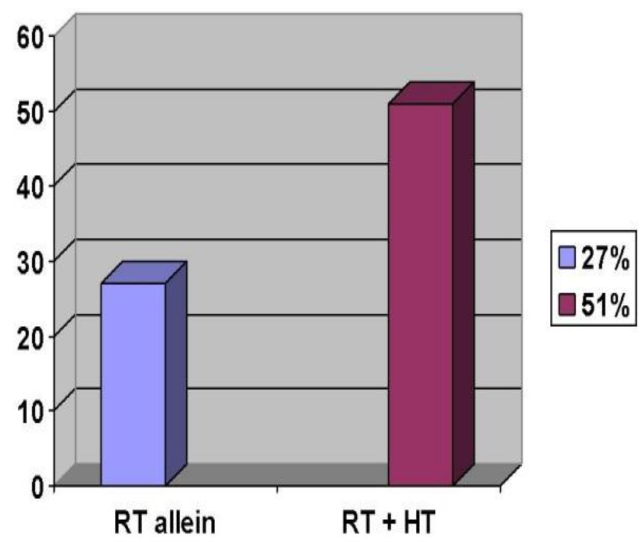


Fig 3. Blood Flow in Normal and Tumoral Tissue During Hyperthermia

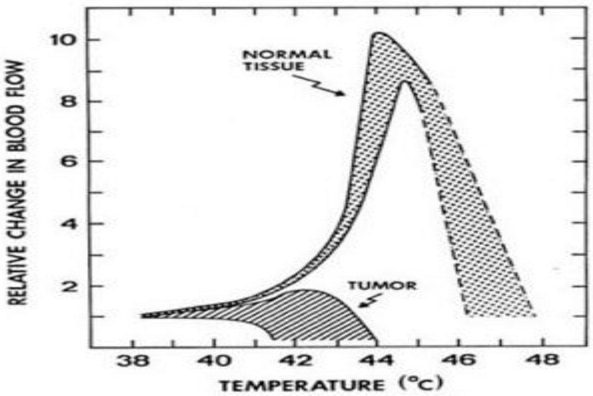
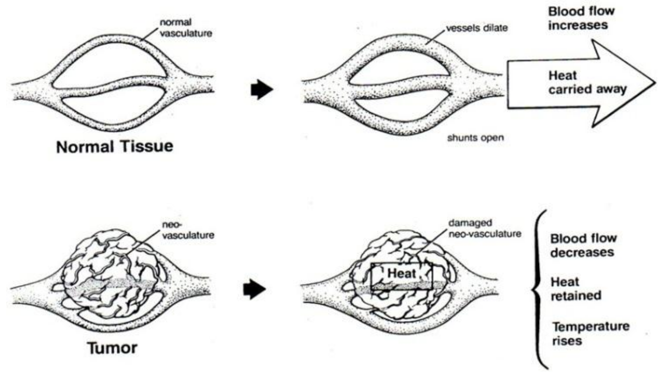


Fig 4. Why Tumors Get Hotter than Normal Surrounding Tissues



Idea courtesy Dr.F.K Storm

Fig 5. Local Hyperthermia

Fig 6. Whole Body Hyperthermia (WBH)

Clifford Hospital China, Joint Commission International

Fig 7. Modern 3D Technique Hyperthermia System

BSD-2000/3D Hyperthermia System

CONCLUSION

The healing power of heat can be used to treat a variety of cancers. Hyperthermia is recognized as new and promising form of cancer therapy in conjunction with surgery, radiotherapy and chemotherapy. Clinical results of research prove that hyperthermia accelerates the antitumor effects of bio therapy, radiation therapy and chemotherapy, however rational use and inclusion of this therapy in standard treatment regimen should also be considered. As the success of this technique depends on where and when this treatment has to be used which needs constant observation and further investigation for research. Constant promotion of research for hyperthermia treatment is the need of the hour. Oncologists' reports and findings shared in research repositories on survival rate, response rate and tumor resistance rate is vital to completely understand and to utilize for better treatment in the fight against cancer.

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