

Principles, applications, risks and benefits of therapeutic hyperthermia

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1. ABSTRACT

Hyperthermia as a heat therapy is the procedure of raising the temperature of a part of or the whole body above normal for a certain period of time. Based largely on delivery methods, therapeutic hyperthermia falls under three major categories: local, regional, and whole-body. It may be applied alone or jointly with other modalities such as radiotherapy, chemotherapy, radiochemotherapy, and gene therapy. Because of the individual characteristics of each type of treatment, different types of heating systems have evolved. This paper provides an overview of possible mechanisms of heat-induced cell death and the way heating exerts its beneficial effect. It also discusses various heating devices as well as other modalities used with hyperthermia. The paper concludes with a summary of benefits and risks, obstacles encountered in the treatment process, and future research directions.

2. INTRODUCTION

Hyperthermia is a heat technique that broadly refers to the treatment of a disease by the application of heat (1). Heat as a therapeutic modality is ancient, but is currently a rapidly developing technique in tumor therapy. Greek and Roman physicians thought that if they could simply control body temperature, they could cure all diseases (2). The amount of temperature elevation is on the order of a few degrees above normal temperature (41-45°C). Temperatures applied in the above range are lethal to malignant cells, while not damaging normal cells. The therapeutic effect of hyperthermia on malignant and normal tissue may vary according to the vascular characteristics of the tumor. The different characteristics of the blood supply among various types of tumors may also explain the differential response of hyperthermia for different types of malignancies.

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The effect of hyperthermia depends on the degree of temperature elevation and the length of time that the elevated temperature is maintained. First, there is the curative, physiologically based therapy (physiological hyperthermia), which treats aches, pains, strains, and sprains. This is applied in multiple sessions, uses low temperatures (for example, below 41°C) for approximately an hour, has a reparative goal of accelerated tissue healing, and makes use of physiological mechanisms of increasing blood flow and metabolic rates (3). At temperatures above 42.5-43.0°C, the exposure time can be halved with each 1°C temperature increase to give an equivalent cell kill (4). Most normal tissues are undamaged by treatment for 1 hour at a temperature of up to 44°C (5).

Hyperthermia as a local therapy offers an effective approach for the treatment of cancer because it is associated with fewer side effects in comparison with chemotherapy and radiotherapy, and it may be used in combination with other treatment modalities. The first paper on hyperthermia was published in 1886 (6). According to the author, the sarcoma that occurred on the face of a 43-year-old lady was cured when a fever was caused by erysipelas. Westermarck (7) used high-temperature water for the treatment of an inoperable cancer of the uterine cervix, and confirmed the effectiveness of this treatment. In the early twentieth century, applied research was carried out in conjunction with basic research; however, since the heating method and the temperature-measuring technology were not sufficiently well developed at that time, the positive clinical application of hyperthermia treatment was not carried out. As a consequence, surgery, radiotherapy, and chemotherapy remained the dominant therapy for tumors (8).

Worldwide interest in hyperthermia was stimulated by the first international congress on hyperthermic oncology in Washington in 1975. In the United States, a hyperthermia group was formed in 1981, followed by the European Hyperthermia Institute in 1983. In Japan, hyperthermia research began in 1978 and the Japanese Society of Hyperthermia Oncology was established in 1984. This interest has followed a course that is usual for a new type of treatment. Several investigations have since demonstrated that the improvements in treatment outcome by adjuvant hyperthermia can be substantial, provided that adequate heating procedures are used (9).

Today, different heating modalities are available for hyperthermia. These include: hot packs that increase the temperature of the skin only; infrared energy which produces superficial heating only; radiofrequency (RF) and microwave diathermy that does not overheat the skin, but increases the temperature below the skin surface, keeping the skin temperature under 36°C; and ultrasound, which is not always suitable for hyperthermia, especially in those sites where bone is present, because it generates hot spots and pain and does not increase the blood flow (10).

This article begins by outlining the biological basis for hyperthermia. We then discuss the three major categories of clinical hyperthermia: localized, regional, and whole-body hyperthermia (WBH). Because of the specific characteristics

of each type of treatment, different types of heating systems have evolved. Hyperthermia may be applied alone or jointly with other treatment modalities such as radiotherapy, chemotherapy, radiochemotherapy, surgical treatment, and gene therapy. The article also discusses the various risks of hyperthermia and concludes with a discussion of challenges and opportunities for the future.

3. BIOLOGICAL BASIS FOR HYPERTHERMIA

The biological rationale for the treatment of malignant disease by heat is motivated by several considerations including: cell survival, which depends on the temperature and duration of heating; developed resistance to subsequent heat following previous heat treatment; differential sensitivity of normal and tumor cells to heat; and enhancement of biological effect of both radiation and chemotherapy agents (2, 8).

3.1. Heat only

In humans, there are three major body temperature ranges: beneficial fever (< 41.8°C), deleterious temperature (> 44°C), and the hyperthermia range (41-44°C). In the hyperthermia range, clinical hyperthermia therapy may exert a beneficial role (defined as destruction of the target tissue, with minimal to no effect on the normal tissue) if malignant tissues are more thermosensitive than normal tissue (11). Cells differ with respect to their thermosensitivity, which depends on cell type and local environment. For example, treatment at temperatures between 40- 44°C is cytotoxic for cells in an environment with a low pO₂ and low pH, conditions that are found specifically within tumor tissue because of insufficient blood perfusion (9).

Heat is a kind of energy, which may be characterized by the specific absorption rate (SAR) in the human body. Practically, heat is pumped up into the targeted system to alter chemical bonds and/or chemical reactions with a view to destroying the malignant cells/tissue. If the energy transfer is optimum, then all pumped-in energy is devoted to changing chemical bonds and to destroying the actual biochemical processes in the malignant tissue (12). Protein damage is the main molecular event underlying the biological effects of hyperthermia within the therapeutic window (41-45°C).

The responses of tumors to hyperthermia involve both cellular and host-related factors. When cells are exposed to high temperatures, they are inactivated in a time- and temperature-dependent fashion. Inactivation starts at 40° to 41°C for murine cells and tumors. At these low temperatures, cell inactivation continues for only a few hours; beyond that time, the surviving cells appear resistant to further exposure to such temperatures. For most rodents, inactivation is exponential with time and thus resembles cell inactivation by ionizing radiation. Human cells tend to be more resistant, and in some human tumor cell lines their temperature threshold is as high as 44.5°C. Hence, thermotolerance can develop during treatment of human lesions, since tumor temperatures only rarely exceed 44°C. At even higher temperatures, thermotolerance does not

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develop, but if the cells are returned to 37°C, the surviving cells become resistant within a few hours (2, 13).

3.2. Heat and radiation

The combination of two therapies into one therapy can produce a wide spectrum of results, ranging from enhanced cell killing to stimulated cellular growth (11). Aggregation of nuclear proteins damage is thought to be the central event by which heat makes cells more sensitive to radiation (14). The synergy between heat and radiation, often expressed as thermal enhancement ratios (TER), is highest when the two modalities are given simultaneously. When heat precedes radiation, the synergy is lost if the time interval between the two modalities increases; this loss of TER nicely parallels the decline in protein aggregation. It is important to note that at the time when TER is maximal (during or immediately after heating) heat shock protein (HSP) levels have not yet increased; inversely, when HSP levels are maximal, cells have regained normal radiosensitivity. This implies that HSPs are not involved in thermal radiosensitization and they do become less well radiosensitized than non-thermotolerance control cells and the decline of radiosensitization is more rapid as if cells have been heated with a milder heat treatment. This is because in the thermotolerance cells, nuclear protein aggregation is attenuated and/or repaired more rapidly due to the elevated HSP levels (2, 15).

Heat enhances the cytotoxicity of X-rays, in both a greater than additive and a complementary fashion. Supra-additivity refers to increased cytotoxicity, over what would be expected on the basis of additivity of the two treatments and is at its maximum when these are given simultaneously. Supra-additivity diminishes with time when the treatments are separated by more than 1 or 2 hours, and in some systems, even less (2, 16).

3.3. Heat and chemotherapeutic agents

Combination therapy involving the use of heat and drugs is a very attractive treatment option, since the cytotoxic efficiency of several drugs is increased by elevated temperatures. Moreover, heat can cause more than cell killing when combined with selected chemotherapeutic agents such as mitomycin C, nitrosoureas, platinum drugs, and some antibiotics (17), although for some drugs only additive effects or even less than additive effects on cell death are found (18). When cells are exposed at elevated temperatures to drugs, their response is frequently different from that seen at 37°C. Drugs whose rate-limiting reaction is primarily chemical (for example, not involving enzymes) would, on thermodynamic grounds, be expected to be more efficient at higher temperatures. The rates of alkylation of DNA, or of conversion of a nonreactive species to a reactive one, can be expected to increase as the temperature increases. Tissue culture studies have shown this to be true for the nitrosoureas and cisplatin. For other drugs, there appears to be a threshold at or near 43°C. Below that temperature, drug activity is only mildly enhanced. At higher temperatures, however, cell killing proceeds at a greatly enhanced rate (2, 18).

4. TYPES OF CLINICAL HYPERTHERMIA

Prior to discussing types of clinical hyperthermia, it is important to define what is meant by a clinical trial involving hyperthermia. Clinical trials are categorized into three phases. Phase I is a clinical study designed to evaluate the toxicity of the treatment. Phase II is a clinical study designed to evaluate the effectiveness of the therapy. Phase III is clinical study that compares one treatment method with another. Usually a new treatment method is compared to the standard treatment, which acts as the control. The control group may be historical, randomized or nonrandomized within the study.

4.1. Local hyperthermia

The objective of local hyperthermia is to increase the tumor temperature, while sparing surrounding normal tissue, using either external or interstitial modalities. The volume that can be heated depends on the physical characteristics of the energy source and on the type of applicator (19, 20). Candidates for local hyperthermia include chest wall recurrences, superficial malignant melanoma lesions, and lymph node metastases of head and neck tumors.

Local hyperthermia can be applied as external, intraluminal or interstitial treatment. External techniques are used to treat tumours that are in or just below the skin. They may be used alone or in combination with radiation therapy for the treatment of patients with primary or metastatic cutaneous or subcutaneous superficial tumors (including superficial recurrent melanoma, chest wall recurrence of breast cancer, and cervical lymph node metastases from head and neck cancers). Heat is usually applied using energy generated from a source outside the body such as a microwave or ultrasound source, applicator, and a means of measuring temperature in the tumor (Figure 1). Currently, hyperthermia systems can be interfaced with magnetic resonance imaging (MRI) systems, allowing noninvasive temperature monitoring of the treatment.

Intraluminal or endocavitary methods may be used to treat tumors within or near body cavities. Endocavitary antennas are inserted in natural openings of hollow organs. These include: gastrointestinal (esophagus, rectum); gynecological (vagina, cervix, and uterus); genitourinary (prostate, bladder); and (4) pulmonary (trachea, bronchus). Very localized heating is possible with this technique by inserting an endorectal electrode into lumens of the human body to deliver energy and heat to the area directly. Various types of electrodes are available depending on the size of the lumen and the site of the lesion. Interstitial techniques are used to treat tumors deep within the body, such as brain tumors. Imaging techniques, such as ultrasound, may be used to make sure the probe is properly positioned within the tumour (21).

Facilitated by the enormous progression in the application of efficient computational methods, the last decade has witnessed important advances and innovations in the technology needed to develop RF, microwaves and ultrasound applicators. Table 1 compares these three major hyperthermia techniques.

Table 1. Comparison of Major Hyperthermia Techniques

Technique	Advantages	Disadvantages	Application
Ultrasound	Focus in tissue. No hot spots in fatty tissues. Heating capability up to 5-10 cm depth with single source and up to 20 cm depth with multiple sources.	Heating area is small. No penetration of tissue-air interfaces.	Treatment of superficial and deep regional tumors. Examples include surface lesions; head and neck, and lesions in extremities.
Radiofrequency	Simple instrumentation. Large treatment area. Electrodes not limited in size and insulation can be accomplished.	Difficult to control electric fields. Only areas where fat is thin can be treated by capacitive systems. Heating regional with external applicators.	Treatment of large and superficial tumors in neck, limb, chest, brain, abdomen, etc.
Microwaves	Large heating volume. Multiple applicators, coherent or incoherent, can be used. Can avoid hot spots in fatty tissues.	Limited penetration at high frequencies. Temperature measurement is difficult and thermometry requires noninteracting probes.	Treatment of superficial tumors in breast, limb, prostate, brain, etc.

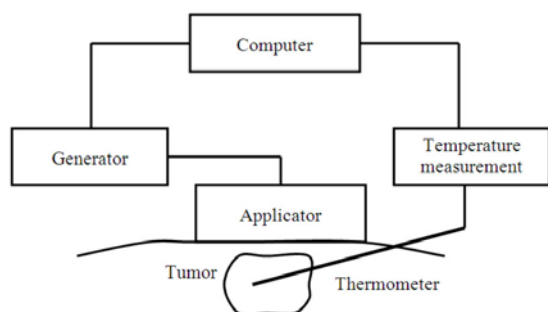


Figure 1. Local hyperthermia system.

4.2. Regional hyperthermia

Regional heating suits patients with locally advanced deep-seated tumors, such as those in the pelvis or abdomen. Deep tissue techniques may be used to treat cancers within the body, such as cervical or bladder cancer. The application of regional hyperthermia is, however, more complex than local heating, particularly because of wide variation in physical and physiological properties. It requires more sophisticated planning, thermometry, and quality assurance. Since regional heating techniques apply energy to the adjacent deep-seated tumors in a focused manner, energy is also delivered to the adjacent normal tissues. Under such conditions, selective heating of tumors is only possible when heat dissipation by blood flow in normal tissue is greater than that in tumor tissue. Most clinical trials on regional hyperthermia have used hyperthermia as an adjunct to radiotherapy. Locally advanced and/or recurrent tumors of the pelvis are the major indications for regional hyperthermia, including rectal carcinoma, cervical carcinoma, bladder carcinoma, prostate carcinoma, or soft tissue sarcoma.

Heat delivery to deep-seated tumors is the most difficult problem and major efforts have been devoted to the development of external deep-heating equipment. External applicators are positioned around the body cavity or organ to be treated, and electromagnetic (EM) energy is focused on the area to raise its temperature. Deep regional hyperthermia is usually performed using an array of multiple applicators. This system has the advantage that subcutaneous fat is not excessively heated, and is thus suitable for obese patients. Nevertheless, this method causes systemic symptoms such as tachycardia and malaise, which result from the use of large-sized applicators. Theoretical model calculations show significant improvements in control of power distribution by increasing the antenna number, under the assumption of

optimum adjustment of phases and amplitudes (21).

Regional perfusion techniques can be used to treat cancers in the arms and legs, such as melanoma or cancer in some organs, including the liver or lung. In this procedure, some of the patient's *blood* is removed, heated, and then pumped (perfused) back into the limb or organ. Anticancer drugs are commonly given during this treatment. Regional hyperthermia is usually applied by perfusion of a limb, organ or body cavity with heated fluids.

4.3. Whole-body hyperthermia

WBH at temperatures up to 42°C is a distinctive and complex pathophysiological condition that has incredible impact on tissue metabolism, blood flow, organ function, and tissue repair. A common characteristic of WBH is that energy is introduced into the body, while at the same time energy losses are minimized. WBH has been investigated since the 1970s as an adjuvant to conventional chemo- or radiotherapy for the treatment of various malignant diseases. It is used to treat metastatic cancer that has spread throughout the body. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumor and surrounding tissue is monitored throughout hyperthermia treatment. Three major methods are now available to achieve reproducible and controlled WBH: thermal conduction (surface heating), extracorporeal induction (blood is pumped out of the patient's body, heated to 42°C or more, then put back in the body while still hot), and radiant or EM induction. The tolerance of liver and brain tissue limits the maximum temperature range for using WBH (41.8°C - 42.0°C), but this temperature may be maintained for several hours (21).

5. HYPERTHERMIA SYSTEMS

The delivery of energy to tumors without overheating the normal tissues is an important prerequisite for the clinical application of hyperthermia. The control of heat transfer deeply into and within the body is a complex issue and is largely dependent on the performance of the equipment used for tissue heating and thermometry including heat applicators (external, intracavitary, and interstitial) and temperature measurement techniques (invasive and noninvasive).

The common physical modalities employed for power deposition in local and regional clinical hyperthermia are ultrasound and EM energy. The basic

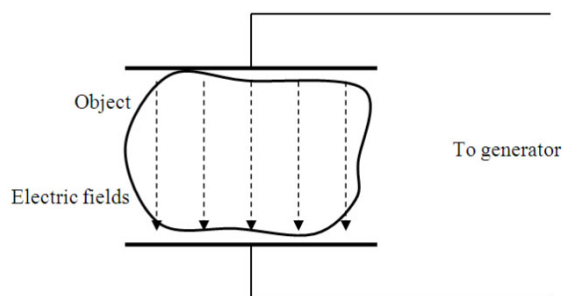


Figure 2. Capacitive applicator for hyperthermia.

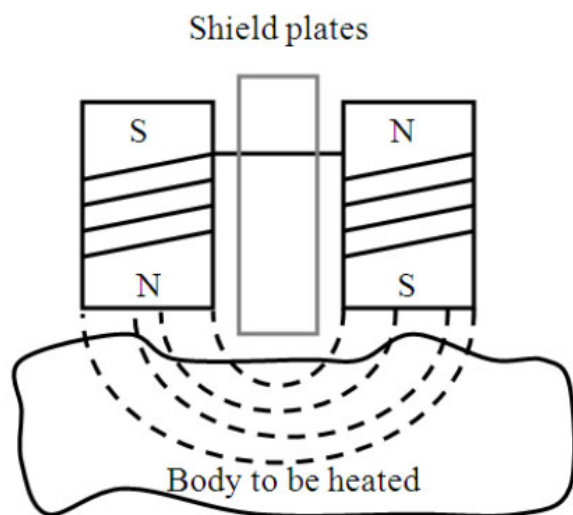


Figure 3. Inductive applicator for hyperthermia.

performance of a particular applicator used to induce clinical hyperthermia may be characterized by its heating efficiency and ability to produce a uniform pattern of heat distribution throughout the tumor.

5.1. Capacitive-inductive-coupling systems

Usually, these applicators operate at industrial, scientific, and medical (ISM) frequencies of 13.56 MHz, 27.12 MHz, and 40 MHz. They are classified in two different configurations. The capacitive-coupling applicator is composed of two-plate capacitor excited by an electric potential between the plates as shown in Figure 2. Capacitive hyperthermia equipment generally consists of an RF generator, an RF power meter, an impedance matching network, a set of electrode applicators, a temperature control system for the applicators, a set of connecting cables, and a patient support assembly. The RF energy is transmitted locally or regionally through interaction of electric fields produced between the parallel-opposed electrodes. The adjustable positions of the electrodes permit heating at different angles and treatment sites (21). RF-capacitive devices are convenient to apply to various anatomical sites where tissues can be heated by displacement currents generated between the two capacitor plates. However, such devices are not robust in terms of

positioning, because currents tend to concentrate around the closer electrode tips when they are nonparallel. Another disadvantage is the excessive heating of subcutaneous fat. This is because electric fields generated are normal to the skin surface and currents must pass through the high-resistance low-blood flow superficial fatty layers causing substantial superficial heating.

An inductive coupled energy transfer from coil carrying alternating current (AC) surrounding a biological object through air is used to achieve deeper (typically more than 5 cm) hyperthermia. Magnetic fields in RF induction heating can penetrate tissues, such as subcutaneous fat, without excessive heating. Such magnetic fields induce eddy currents inside the tissues. Since the induced electric fields are parallel to the tissue interface, heating is maximized in muscle rather than in fat. In general, inductive applicators seem to not couple as strongly to the body as capacitive applicators, and relatively high currents are usually needed to get adequate heating. Subsequent use of these devices shows that they still heat a large amount of normal tissues. An inductive applicator for hyperthermia is shown in Figure 3. A pair of cylindrical ferrite cores is used for the applicator. The distance between the pair is adjustable depending on the size of the region to be heated. The target is placed between or under the ferrite cores. The time-varying magnetic field penetrating the body causes an eddy current. As a result, heat is produced. To effectively control the heating position vertically or horizontally, conductive plates to shield the magnetic field are introduced.

5.2. EM radiation devices

One of the major problems of EM radiation devices is the limited depth of penetration due to the EM principle of skin-depth. Only tumors located 2-3 cm from the skin surface may be heated with conventional surface applicators. Different types of antennas can be used as applicators including waveguides and horns, and microstrip patches.

Early hyperthermia trials were conducted with single aperture devices having no ability to steer or focus energy other than shifting patient position relative to the applicator. The type of applicator selected depends on the production of sufficient thermal field distributions at different depths of the tumor in a variety of anatomical sites. Single-element applicators can safely deliver optimum thermal doses to relatively small superficial tumors. This requires body conformal antennas with a power distribution as homogeneous as possible over the skin area.

To increase the value of SAR at a sharp focusing depth relative to the surface SAR in hyperthermia therapy, an array of applicators must be used. A basic array for external deep heating will likely consist of an annular ring of radiating apertures (Figure 4). The parameters of interest are external electric field within an array at the surface of the patient's body, the SAR pattern within the target volume, and the radiation leakage levels of the scattered fields around the applicator. The array of applicators with

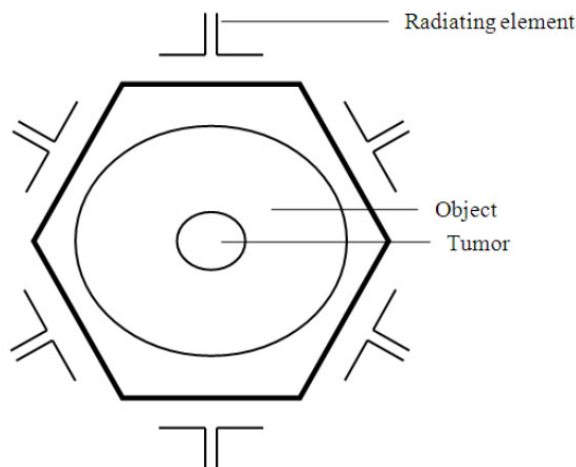


Figure 4. An array of radiating elements for hyperthermia.

variations in phase, frequency, amplitude, and orientation of the applied fields can add more dimensions to controlling the heating patterns during hyperthermia cancer therapy. RF array applicators surrounding the body are used to heat deep tumors. However, studies in external RF array thermotherapy have demonstrated the difficulty of localizing RF energy in malignant tissue deep within the human body without damaging superficial healthy tissue due to hot spots. Improvements in RF energy deposition are achieved when the phased array is controlled by an adaptive algorithm to focus the RF energy in the tumor and tumor margins, while the superficial RF fields are nullified.

Clinically, the use of phased arrays as heating applicators has several advantages. Phased arrays can easily compensate for the effects of inhomogeneities of the treatment volume (which includes the tumor and the surrounding tissues). The heating pattern can be controlled electronically, thus eliminating the need for mechanical movement of the applicator head. This simplifies the machine patient interface and allows for better use of the available power.

5.3. Interstitial and intracavitary devices

As early as 1976 it was suggested that RF currents applied between groups of stainless-steel electrodes could be used to induce elevated temperatures in deep-seated (depth ≥ 3 cm) tumors. The application of an alternating voltage of sufficient magnitude across planes comprising multiple pairs of such electrodes is capable of generating electrical currents through the tumor leading to an increase of the tissue temperature. The simplicity of the basic concept accounts for increasing acceptance of interstitial probes by hyperthermia research groups, and its application to various anatomical tumor-bearing sites (21).

Interstitial hyperthermia is an invasive procedure wherein a single or an array of interstitial antennas or electrodes is implanted in accessible tumors, which might be located in deep or superficial tissues. The invasiveness gives interstitial systems the clear advantage of being potentially effective, therefore potentially maximizing the

tumor temperature while minimizing thermal damage to normal tissue. In addition to electrodes, the interstitial hyperthermia system includes a generator controlled with an automatic tuning system and temperature limitation system. Temperature measurements must be performed at the antennas and between them. In most systems, every single antenna is controlled by its own generator. Dedicated systems have in addition two or more segments per antenna or electrode controlled in phase and/or amplitude (21). One limitation of the interstitial heating system is the inability to vary the power deposition along the radial direction.

Although often compared to interstitial techniques, intracavitary systems are really interior versions of superficial systems that, by using the appropriate body cavities, minimize both the amount of intervening normal tissue between the applicator and the tumor (compared with using a superficial system for the same tumor) and the amount of tissue trauma (compared with the more invasive interstitial system). Intracavitary systems are quite promising for few important sites such as the prostate and the esophagus. Recently, more advanced techniques have been developed, including multiple applicators in a segmented, phased array ultrasound system (3).

5.4. Magnetic fluid hyperthermia

Magnetic fluids are increasingly used for clinical applications such as drug delivery, MRI, and magnetic fluid hyperthermia (MFH). The latter technique, which has been available as a cancer treatment for several decades, involves the injection of magnetic nanoparticles into tumors and their subsequent heating in an alternating magnetic field (22). The idea is to introduce magnetic particles into a malignant tumor and to increase the interstitial temperature by alternating magnetic fields to eliminate the tumor. This technique meets the requirement of maximal deposition of heat within the targeted region under maximal protection of the surrounding healthy tissue.

For clinical applications, magnetic materials should present low levels of toxicity, as well as a high saturation magnetic moment in order to minimize the doses required for temperature increase. Currently, magnetite (Fe_3O_4) is used in this process because it presents a high Curie temperature, high saturation magnetic moment (90-98 emu/g, or ~ 450 -500 emu/cm³), and has shown the lowest toxicity index in pre-clinical tests.

One particular advantage of MFH is the option to plan the magnetic fluid distribution prospectively and to calculate the heat distribution to a highly reliable degree thereafter, due to the density distribution of the nanoparticles in post instillation computerized tomography (CT) and the known SAR of the particles. This was confirmed by experimental data showing that about 90% of the injected amount of iron was detectable by CT in tissue samples (23). The stability of the nanoparticle deposits is regarded as another advantage of the method. In an animal model of prostate cancer, it was demonstrated that 10 days after injection of the magnetic fluid, almost 90% of the dose of ferrites was still detectable in the tumor (24). Even

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one year after application, the particles are still detectable by CT. Thus, repeated treatments over an extended long time period spanning several weeks are possible without additional injection of the magnetic fluid, enabling its inclusion in multimodal treatment options.

An inconvenient aspect of the method is that patients with metallic implants (for example, artificial hip joints) within 30 cm from the treatment area have to be excluded from treatment. Dental amalgams or gold crowns have to be replaced by ceramics, before the treatment of head and neck cancer. Metallic clips or seeds several millimeters in length and less than 1 mm in diameter are permitted due to their very low power absorption capacities. Patients with cardiac pacemakers and implanted defibrillators are excluded from the application of this therapy (21).

6. HYPERTHERMIA WITH OTHER MODALITIES

The most beneficial contribution of hyperthermia for oncological treatments will be based on enhancing the effectiveness of various treatment modalities, such as radiotherapy, chemotherapy, radiochemotherapy, and gene therapy.

6.1. Hyperthermia and radiation

As noted previously, the synergistic effects of hyperthermia combined with radiation have been investigated and reported to yield more complete and durable responses than radiation alone in superficial tumors. Several mechanisms are responsible for the supra-additive effect of the combination of radiotherapy and hyperthermia. The additive complementary effect comes from the sensitivity of cells in the hypoxic, low pH areas, and the cells in S-phase, which are both relatively radioresistant (4). Hyperthermia may cause an increased blood flow, which may result in an improvement of tissue oxygenation, which then results in a temporally increased radiosensitivity. Accordingly, this combined treatment might be considered effective, especially for patients who are unfit to receive chemotherapy

Hyperthermia therapy can substantially improve local tumor control, tumor clinical response, and survival rates after radiation therapy, without a significant increase in side-effects (25). Many clinical trials showed considerable therapeutic gain compared to radiation alone in treating various cancerous tumors and provided long-term improvement in local control and survival without inducing serious side effects (26-30). However, not all research studies have shown increased survival in patients receiving the combined treatments (31, 32). Recently, Franckena and van der Zee (33) reviewed the literature on the clinical use of combined radiation and hyperthermia for gynecologic malignancies. The authors recommended combined radiation and hyperthermia as an alternative to chemoradiation for patients with locally advanced cervix cancer and be the first treatment of choice for these patients when radiation cannot be combined with chemotherapy. For other patients, the optimal treatment combination is currently being investigated in randomized clinical trials.

6.2. Hyperthermia and chemotherapy

The main benefit of hyperthermia to chemotherapy is the fact that hyperthermia shows synergy with some drugs against cancer cells. Hyperthermia may be helpful in preventing or delaying the development of tumor resistance to a given chemotherapy drug or in reversing the acquired resistance of a tumor to a given therapeutic drug (34). Hyperthermia combined with chemotherapy appears to result in increased cell toxicity due to a net increase in DNA damage after exposure to hyperthermia and chemotherapy. Elevated cell tissue temperature, induced by EM energy absorption, significantly enhances the effectiveness of chemotherapy in the treatment of malignant tumors in the human body without increasing the infused amount of drug.

The important mechanisms for an interactive effect are an increased intracellular drug uptake, enhanced DNA damage, and higher intratumor drug concentrations, resulting from an increase in blood flow. An interactive effect was observed for virtually all cell lines treated at temperatures above 40°C for alkylating agents, nitrosureas, and platin analogues, with enhancement ratios depending on temperature and exposure time. The effect of these drugs can be enhanced by a factor of 1.2 to 10; an extremely high thermal enhancement ratio of 23 was even observed for *in vitro* application of melphalan to drug-resistant cells at 44°C [9]. In combination with chemotherapy, the type of drug, dose, temperature and time of administration all play a role in determining the effectiveness of therapeutic hyperthermia.

Improvement of local control and efficacy of multimodality treatment with chemotherapy and hyperthermia have been reported by many investigators (35-37). However, phase III trials are needed to fully evaluate this treatment modality.

6.3. Hyperthermia and radiochemotherapy

Radiochemotherapy is a widely used technique of treatment for patients suffering from primary, locally advanced, or recurrent rectal cancer. The efficacy of treatment can be enhanced by additional application of regional hyperthermia to this conventional therapy regime. The feasibility and efficacy of radiochemotherapy with hyperthermia in the treatment of many types of cancer have been reported in recent papers (38-41). Radiochemotherapy may benefit from the addition of hyperthermia in increasing survival and quality of life, without increasing the risk of complications (41). Further research is required to compare radiochemotherapy versus radiochemotherapy plus hyperthermia in controlled clinical trials.

6.4. Hyperthermia and gene therapy

Gene therapy is a treatment in which genetic material is introduced in a cell to enhance or modify its function. This results in the manufacture of proteins which are either directly therapeutic or interact with other substances to exert a therapeutic effect. In order to treat cancer effectively, the genetic material must exert its effect only on tumor or tumor-associated cells, not on normal cells, and must not eliminate the body's immune response

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that is so critical in fighting cancer. In order to achieve these goals, an approach must be developed that combines fever-range WBH with a gene that only affects tumor cells spliced with additional genetic material designed to cause the suicide gene to be expressed predominantly in tumor cells. Hyperthermia is expected to help in opening up the pores of blood vessels in tumors so that more liposomes reach the tumors and deliver their DNA content to tumor cells. It also increases the amount of protein created by the incorporated DNA and boosts the immune system so that it sends specialized cells into the tumors to help kill them. Research investigation found that gene-infected cells are more sensitive to hyperthermia or to hyperthermia combined with radiation with no apparent systemic toxicity (42, 43).

7. HYPERTHERMIA TREATMENT PLANNING

Hyperthermia treatment planning (HTP) is needed to design, control, document, and evaluate a treatment and to provide the required data for treatment optimization and the insight to design better heating devices. The aim of HTP is to determine control parameters in such a way that a favorable temperature distribution is achieved. Such a distribution can be characterized by the requirements that the heating should be concentrated in the tumor and hot spots should be avoided in healthy tissues. Numerical techniques act as a core of absorbed power computations needed in the HTP (44).

The ability to measure temperature rise within the patient is important for all thermal treatments and HTP will ultimately provide information about the actual temperature distributions obtained and thus the tumor control probabilities to be expected. This will increase the understanding of the clinical results of thermal therapy, and will help both in optimizing clinical heating technology and in designing optimal clinical trials (45). While a great deal of effort is applied toward solving the technical problems associated with modeling clinical thermal therapy treatments, especially on estimating the power deposition, other efforts should be applied toward using the modeled power depositions as inputs to estimate the thermal therapy induced 3D temperature distributions. The type of treatment planning programs that have already been developed for radiotherapy must be developed for more complex requirements of both prospective and retrospective study of thermal dosimetry in clinical thermal therapy (44).

As a comprehensive process, HTP includes: (a) methods for the determination of the target volume (target definition), (b) segmenting medical image data, generating of 3D model of the target and normal tissue structures, (c) calculating the absorbed power distribution, (d) assigning tissue thermal properties, (e) virtually placing heat sources into the 3D structure, (f) measuring SAR patterns, and (g) calculating heat transfer from the solution of bioheat equation during treatment from the power deposition to provide temperature distribution as a function of time. An important feature of the thermal model is its capability to describe the complex heat transfer related to the vasculature (44, 45).

Based on the results of temperature calculation, optimal applicator parameters including amplitudes and phases of the signals sent to the antennas are determined. In the case of the nonlinear bioheat equation, temperature calculation and optimization are coupled via a fixed-point iteration. For treatment planning or post treatment evaluation of completed therapy, a more detailed study of the dielectric parameters, anatomical structures, and blood perfusion mechanisms is necessary. Monitoring and control of temperatures during treatment requires advanced thermal imaging (44).

8. BENEFITS, RISKS, AND OBSTACLES

8.1. Summary of benefits

Hyperthermia exerts its beneficial effect in several ways. Heat causes various changes in tissue physiology such as regional increase in the blood flow, vascular permeability, and metabolic activity. The most important physiological parameter in this context is blood flow. When tissues are heated, various physiological changes occur, the majority of which are secondary to changes in blood flow (1). Hyperthermia induces a general increase in the metabolic rate (46), as most enzymes enhance their activity when temperature rises. As a consequence, tissue locally increases its oxygen consumption, and hyperthermia enhances oxygen contribution to the heated site (11). Since blood flow is one of the major vehicles by which heat is dissipated from tissues, blood supply to tissues will have a significant influence on the ability to heat those tissues (47). Hyperthermia produces an increase in nutrients and oxygen in the heated region. Both nutrients and oxygen are critical for any of the anabolic processes that take place in an organism, and are necessary for tissue repair (11).

In response to heat, hyperthermia enhances apoptosis (48), with the production and secretion of cytokines that induce a strong stimulus for repair (49). Heat improves the contractile performance of muscle, as it increases ATPase activity and changes the mechanical properties of collagen in tendons (50). Hyperthermia may affect pain sensation, producing an alteration in sensory nerve response. Two major hypotheses have been advanced to explain the analgesic effect of hyperthermia, namely, the metabolic and the neurological hypotheses. According to the metabolic hypothesis, analgesia is produced by washing out inflammatory mediators from the area of injury (51). This would interrupt stimuli to the free nerve endings responsible for pain. The metabolic hypothesis would explain the analgesic effect of hyperthermia in acute pain, whereas in chronic pain, non-myelinated c-type neuronal fibers are mainly involved. In this instance, pain is due to hyperexcitability of the local painful stimuli conduction system (neuroaxial pain) or to altered peripheral spinal gating. Experimental studies on the analgesic effect of hyperthermia in chronic pain showed that the pain conduction velocity on the sciatic nerve is markedly reduced for approximately 60 minutes after a hyperthermia session. This reduction in conduction velocity can indirectly produce a decrease in the pool of signals carrying pain stimuli, allowing reset of the gate control at the spinal level (52).

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Therapeutic hyperthermia might also activate the immune system causing both increased production of interferon alpha, and increased immune surveillance. Immuno-stimulation by hyperthermia involves both direct effects of heat on the behavior of immune cells as well as indirect effects mediated through HSP release. In addition, HSP can be deployed as components of antitumor vaccines in protocols that do not include hyperthermia. Understanding this process may permit the effective deployment of hyperthermia and HSP based vaccines in tumor treatment (53). In a recent review, Torigoe *et al.* (54) discussed different aspects of the roles of HSP in immunity and the therapeutic application of hyperthermia for immuno-modulation.

Takahashi *et al.* (55) suggested that hyperthermia as an inexpensive and less-invasive conservative therapy can be effectively applied to the treatment of osteoarthritis. Heat stimulation by EM waves to the joints can increase HSP70 expression in chondrocytes; at the same time, HSP70 expression partially enhances matrix metabolism of the cartilage of joints.

8.2. Summary of risks

The toxicity of heat generated during hyperthermia is generally low. Pain and burn represent typical hyperthermia associated risks that may be minimized or avoided via correct heating techniques. The primary hazards of hyperthermia are due to either increased body core temperature or increased temperature in specific organs. When body temperature rises, heat balance of the body is normally restored by increased blood flow to the skin and by sweating. These responses increase the work of the heart and cause loss of salt and water from the body. They impair working efficiency and can overload the heart and cause haemoconcentration, which may lead to coronary and cerebral thrombosis, particularly in elderly people with atheromatous arteries. Most healthy people can tolerate body core temperature excursions up to 40°C when adequately hydrated. At higher temperatures (42 to 43°C) cell death may occur (56).

The biological mechanisms by which hyperthermia may induce adverse health effects are still under investigation. Increases in temperature result in increases in molecular motion in cells, tissues, and organs. This increased molecular motion in turn increases chemical reaction rates. If reaction rates within steps of a metabolic process become unbalanced, metabolism may be altered. The activation energies of metabolic reactions are low, of the order of 3-20 kcal/mole. For short duration heat exposures, it is thought that unbalanced metabolism would be transitory, and therefore, unlikely to cause permanent damage. Long periods of unbalanced metabolism could cause permanent, irreversible damage, although there is currently no scientific evidence for this hypothesis (57).

Pathological changes can be observed in the nerve cells and glial cells in humans following mild to moderate thermal exposure. Morphological changes in the axons, nerve cells, glial cells and vascular endothelium are seen at the cellular and the molecular levels in rats subjected to heat

exposure at 38°C for 4 hours. This effect depends on the age of the animals and their prior thermal experiences. Together, heat stress induced hyperthermia, once believed to be non-toxic in the mammalian central nervous system (CNS), do produce specific alterations in the CNS that may have long-term behavioral, physiological and neuropathological consequences (57). The limited clinical experience to date suggests that safe hyperthermic treatment of CNS malignancies or tumors located close to the CNS is feasible under appropriate technical conditions with adequate thermometry, taking the sensitivity of the surrounding normal nervous tissue into account (58). Application of heat to the peripheral nerves should not be in excess of doses of 30 min at 44 °C or equivalent (59).

Although hyperthermia alone is not carcinogenic, hyperthermia may enhance the development of tumours induced by ionizing radiation or chemical carcinogens; thus, there is the potential for modulation of carcinogenic effects of those agents (60-62). The controversy over whether EM radiation might initiate or promote cancer continues to receive a great deal of attention, both in the popular press and in the biomedical literature (63). Conflicting reports, suggest that hyperthermia treatment (via a water bath) can either serve as an antipromoter (64, 65) or as a promoter (66), depending on the treatment regimen.

The nervous tissues appear critically sensitive to heat with a possibility of damage and changes in nerve morphology for nerve conduction and nerve function (67). Although interspecies differences may play a role in determining sensitivity, the data indicate that the maximum heat dose without obvious complications after localized hyperthermia in regions of the CNS lies in the range of 40–60 min at 42–42.5°C or 10–30 min at 43°C (68).

In 2002, the World Health Organization (WHO) workshop on “Adverse Temperature Levels in the Human Body” brought together scientists with expertise in biological effects of hyperthermia to review the data that could be used to evaluate potential adverse effects from human exposures to RF radiation in the range of 10-300 GHz. Risks to a variety of organs were considered. Thresholds for effects on developing embryos and fetuses and possible carcinogenic effects were also examined. The experts judged the relevance of each study for informing decision-makers about the scientific basis for establishing safe exposure levels. The conclusion was that standards should consider both temperature and time of exposure, whenever possible (69).

8.3. Obstacles

The biological effects of hyperthermia are impressive, but physical heat delivery remains problematic. There is a tendency to blame the “physics” (meaning technical insufficiency) for inadequate treatments in the field of oncological hyperthermia: “The biology is with us, the physics are against us” (70). Like many other early-stage therapies, hyperthermia suffers from lack of adequate technical solutions, treatment experience, quality assurance, and standardization (12, 21). The lack of needed technical solutions and engineering tools may be viewed as a major barrier to hyperthermia’s effective clinical implementation.

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Developing clinically effective systems will be difficult, however, because (a) it requires solving several complex engineering problems, for which (b) setting appropriate design and evaluation goals is currently difficult owing to a lack of critical biological, physiological, and clinical knowledge (3).

Another obstacle for the acceptance of hyperthermia may be that it lacks public awareness. Most of the clinical studies with hyperthermia involve its combination with radiotherapy or chemotherapy. However, the limited experimental and clinical studies with combined chemotherapy and hyperthermia suggest that this combination therapy is also worth further testing (10). Carefully conducted Phase III trials with rigorous quality assurance must employ prospective thermal dosimetry to validate the role of hyperthermia in therapies involving multiple modalities.

A number of challenges must be overcome before hyperthermia can be considered a standard treatment for cancer (2, 10). Hyperthermia suffers from a lack of what constitutes a “dose” of “therapeutic heat”, and a clear understanding of thermometry, treatment standardization, and scientific consensus about its effects on malignant and healthy tissues (11). There is no clear clinical thermal dose effect relationship, which is compounded by the inability to produce consistently a uniform pattern of heat distribution throughout the tumor mass. In order for hyperthermia to gain widespread acceptance and incorporation into clinical use, the technique requires standardization of equipment. Thermal dosimetry is also a challenge, due to the inability to predict or measure accurately the temperature throughout the tumor mass and the surrounding healthy tissues (19, 20).

9. PERSPECTIVE

The usefulness of hyperthermia as a potential treatment modality for cancer requires further investigation in order to elucidate the mechanism actions by which hyperthermia is beneficial in a clinical setting to treat tumors (3). A better understanding of how hyperthermia alters cellular processes relevant to therapeutic endpoints will facilitate more effective deployment of hyperthermia as a therapeutic adjuvant (71). Until the underlying mechanisms are understood and the spatial and temporal distributions of the important biological and physiological variables are known, it will be difficult to set precise engineering design goals (11).

Recent developments in hyperthermia have expanded the treatment options of patients with certain types of cancer. The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. Control of the heating process as a major part of hyperthermia should be improved to ensure that increased temperature levels can be properly maintained, delivered, and localized within the tumor region. To effectively control heating distribution will require (a) sophisticated controllers that can properly steer the power deposition to achieve close-to-optimal

temperatures, and (b) accurate measurements of the spatial and temporal distributions of temperature during treatment.

Thermometry and imaging techniques represent another exciting and challenging future for biomedical engineering. Techniques and modalities, which were only in the experimental research phase in the early 1970s and 1980s, have now become accepted clinical procedures world-wide. These include CT, MRI, ultrasound, microwaves, and terahertz (THz) techniques. Successful noninvasive thermometry may open the door to widespread use of hyperthermia. Simulation tools that incorporate electromagnetically realistic models of the human body including the significant thermal effects of blood perfusion will greatly aid in improving the predictability of temperature distributions in the target volume.

Finally, the development of hyperthermia as a potentially effective treatment for cancer, particularly in combination with other traditional therapies, provides an example of how biomedical engineering can contribute to new treatment modalities.

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Key Words Hyperthermia, Heating techniques, Treatment modalities, Treatment planning, Benefits and risks

Abbreviations: RF: radiofrequency; WBH: whole-body hyperthermia; SAR: specific absorption rate; TER: thermal enhancement ratio; HSP: heat shock protein; MRI: magnetic resonance imaging; EM: electromagnetic; AC: alternating current; MFH: magnetic fluid hyperthermia; HTP: hyperthermia treatment planning; WHO: World Health Organization; CT: computerized tomography; THz: terahertz.

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