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A Technical Review On Hyperthermia

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ABSTRACT:

Hyperthermia has promising strategy to enhance apoptosis .The fundamental idea and the effects of heat on cancer cells are well known. However, the results obtained in therapy by hyperthermia (HT) alone have been only partially satisfactory. Treatment at temperatures between 40 and 44 °C is cytotoxic for cells in an environment with a low oxygen partial pressure and low pH, conditions that are found specifically within tumour tissues, due to insufficient blood perfusion. Under such conditions radiotherapy is less effective, and systemically applied cytotoxic agents will reach such areas in lower concentration than in well-per fused areas. Therefore, clinically it is preferred to use hyperthermia in combination with radiation therapy and chemotherapy. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources; regional hyperthermia by perfusion of organs or limbs or by irrigation of body cavities; and whole body hyperthermia. Which can be implemented by many heating methods, such as microwave, radiofrequency, laser and ultrasound. Number of studies have reported the combination of thermo-radiotherapy. Fortunately, phase II, III clinical trials have demonstrated that hyperthermia combination therapy is beneficial for local tumour control and survival in patients with high-risk tumours of different types. Consequently, much attention has been focussed on identifying agents among the conventional chemotherapeutics substances that can sensitise tumour cells to hyperthermia-induced damage with minimal effects on normal cells. In the review, we overviewed important mechanism of hyperthermia-induced apoptosis and the substance which can act as heat sensitizers' in cancer therapy.

KEYWORDS: Hyperthermia, radiotherapy, chemotherapy, microwave, ultrasound.

I.INTRODUCTION:

Heat are used in many cultures for almost any disease including cancer, first case of a patient with a breast tumor treated with hyperthermia was described more than 3,500 years ago. In 1866 a case was described where sarcoma disappeared after prolonged infection with a high fever causing bacteria. 1898 marked regression of carcinomas of the uterine cervix after local hyperthermia. Hyperthermia refers to an elevated body temperature(T_b) and is commonly categorized as mild (T_b=37.7-39.4 ^oC) to severe (T_b usually greater than 40 ^oC)[1]. Some degree of hyperthermia

accompanies exertional heat illnesses such as heat cramps, heat exhaustion, ans heat stroke. A recent review of the literature revealed that signs of exertional heat illness included confusion, altered state of consciousness, decreased mantal acuity, and an overall decrease in central nervous system function.[2]

Between 1960 and 2003 , heat stroke, resulting in severe hyperthermia, has been the cause of 101 deaths in young American football players with 21 occurring in the last eight years. Since 1974 a dramatic reduction in heat stroke deaths has been observed with the exception of 1978, 1995,1998, when there were four each years, and 2000 when there were five.[3] In the southeastern united states, athletic events occur in hot, humid environment throughout the spring and summer months into the early fall. The average south Florida temperature between environmental factors, football uniforms contributes significantly to the heat load on a players. T_b in football players during an actual football practice fluctuates with activity and with level of equipment worn. T_b increases during the periods of intense exertion with full equipment, and decrease during rest periods.[5] theses conditions are considered unsafe for football activities by the Inter-Association Task Force on Exertional Heat Illness Consensus Statement. The recommendations include a work/rest radio of 15-20 min of work to 5-10min for water/rest break and practices should be in shorts only.[6]

Excessive heat retention causes changes in brain function and metabolism.[7-9] the underlying link between the thermal information processing system (located in the hypothalamus) of the central nervous system, hyperthermia and brain dysfunction is not clearly understood; however; it appears that the extent of nervous tissue injury depends on the duration and intensity of heat exposure. Increased permeability of the blood-brain barrier allows brain edema formation. This breakdown of the blood-brain barrier is similar in nature to what occurs to the central nervous system following trauma indicating that signs and symptoms of hyperthermia can mimic a concussion.

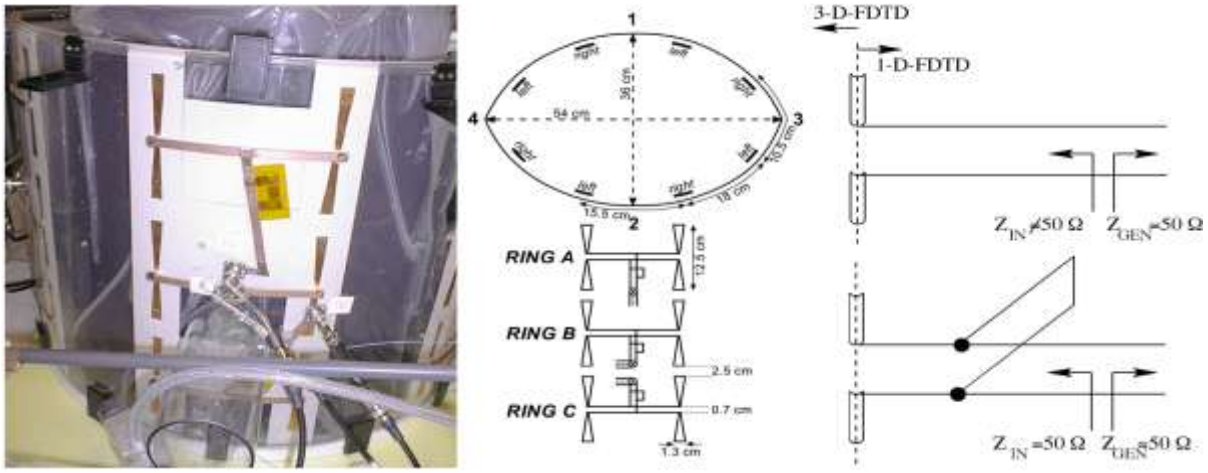
Furthermore, the literature is lacking research in regards to how active hyperthermia influences cognition in physically active males. Since American football practices occur in hot, humid environments it is important that athletic trainers understand and recognized subtle changes in mental performance that accompany hyperthermia in order to make more educated decisions regarding player safety and sport performance. To our knowledge our study was the first to use this tool to identify the effects of active hyperthermia on cognition in a hot , humid environment. Therefore, the purpose of this study was to examine the effects of active hyperthermia on cognitive performance, using hyperthermia^{TM} cognitive stability Index(CSI) , in physically active metals.

II.HEAT GENERATION:

The present technology for deep-body heating based on annular phased arrays (APA) of radiation, which are arranged in a single ring (2-D applicators) or in three rings (3-D applicators) . A commercially available 3-D HT applicators is the 3-D Sigma-Eye from BSD medical corp. (Salt lake city, UT, USA), operating at 100 MHz. antennas of this applicators are electrically short and therefore they need matching circuitry to be inserted between the antenna feed-points and the amplifiers (fig 1). As the power is coupled between the antennas and the impedance matching networks, the matching circuitry must be modelled and taken into consideration, when planning HT treatment (Fig 2). Numerical models excluding the impedance matching networks are not able to predict correctly distributions of E-field, specific absorption rate(SAR) and temperature in Sigma-Eye applicator[10].

To omit problem with external impedance matching circuits we developed a novel 3-D HT applicators based on the concepts of water-coated antennas (WACOA). The outstanding features of this applicators are this applicators are its flexible matching between 100 and 150 MHz by

mechanical adjustments, current balance and high efficiency. In additional, the WACOA applicator can be numerically and is MR compatible.



(a) (b) (c)

Fig. 1. 3-D Sigma-Eye applicator: flat bow-tie dipoles with striplines shunted in Y-junctions are followed by striplines and stubs (a); schematic representation of transversal and longitudinal arrangement of antennas (b); phenomenological 3-D/1-D FDTD model of antenna with its matching circuitry (c).

III.TYPES OF HYPERTHERMIA:

Hyperthermia is mostly applied within a department of radiation oncology under the authority of a radiation oncologist and medical physicist. Hyperthermia is always implemented as part of a multimodal, oncological treatment strategy, i.e., in combination with radiotherapy or chemotherapy.[11] The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissues characteristics[12-45]. 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[46,47] .The majority of hyperthermia treatments are applied using external devices, employing energy transfer by EM technologies[48,49].

A.LOCAL HYPERTHERMIA:

BLATION: Where tumors are literally ‘burned’ or ‘fried’ using specific ,medically guided techniques.
LOCO-REGIONAL(LRHT): Where specific tumor site or parts of tge body or organs are heated using a specialized medical device reaching temperature above 39c to 44c which can either directly cause to damage to cancer .
EXTERNAL**:** Approaches are used to treat tumors that are in or just below the skin . External applicators are positioned around are positioned around or near the appropriate region,and energy is focused on tumor to raise its temperature.
Intraluminal or endocavitary: methods may be used to treat tumors within or near body cavities ,such as

the esophagus or rectum. Probes are placed into the tumor to deliver energy and heat the area directly.

Interstitial techniques are used to treat tumors deep within the body ,such as brain tumors.

This technique allos te tumor to be heated to higher temperatures than external techniques .under **anesthesia, probes or** needles are inserted onto 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.

PERFUSION: Where the blood is specifically heated and circulated either in a specific region of the body.

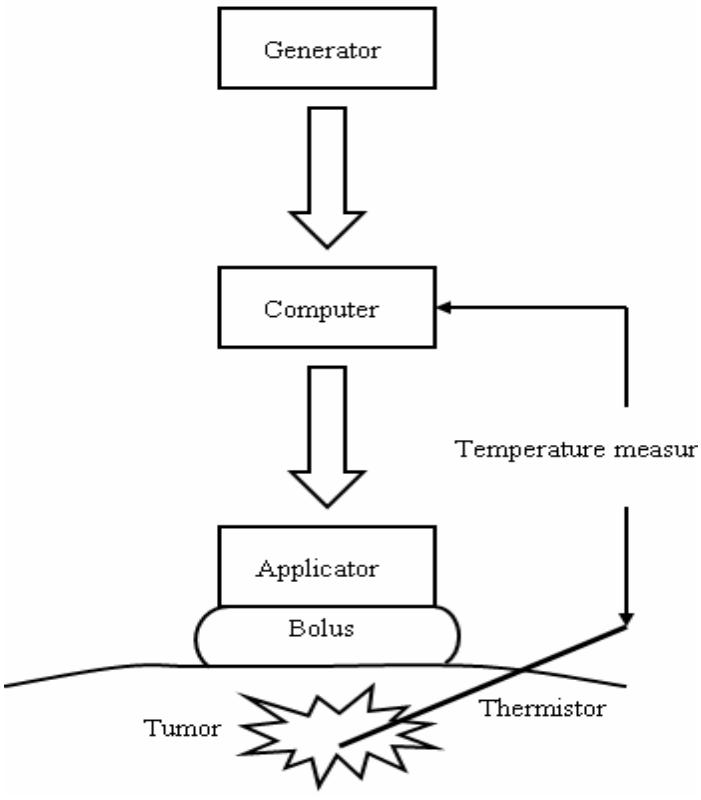


FIGURE 2. A diagram for local hyperthermia

B.WHOLE BODY HYPERTHERMIA(WBH).

The body is stimulated to fight disease. Body temperature can be raised by using warm-water blankets, warm-water immersion (putting the patient in warm water), inductive coils (like those in electric blankets), or thermal chambers (much like large incubators). The body temperature may be raised to about the level a person would have if they had a fever, which is sometimes called *fever-range hyperthermia*. A few studies take the body temperature higher, around 107° F, for short periods of time. At least one human study suggests that this may cause certain immune cells to become more active for the next few hours. Other studies are testing hyperthermia and chemotherapy along with other treatments that are designed to boost the activity of the person's immune system.

Three major methods are now available to achieve reproducible, controlled WBH, namely, thermal conduction (surface heating), extracorporeal induction(blood is pumped out of the patients's body, heated to 42ºC or more , then put back I the body while still hot), and radiant or EM induction[58,60] The tolerance of liver nd brain tissues limits the maximum temperatre for using WBH to 41.8-42.0^{O}C, but this temperature can be maintained for several hours.

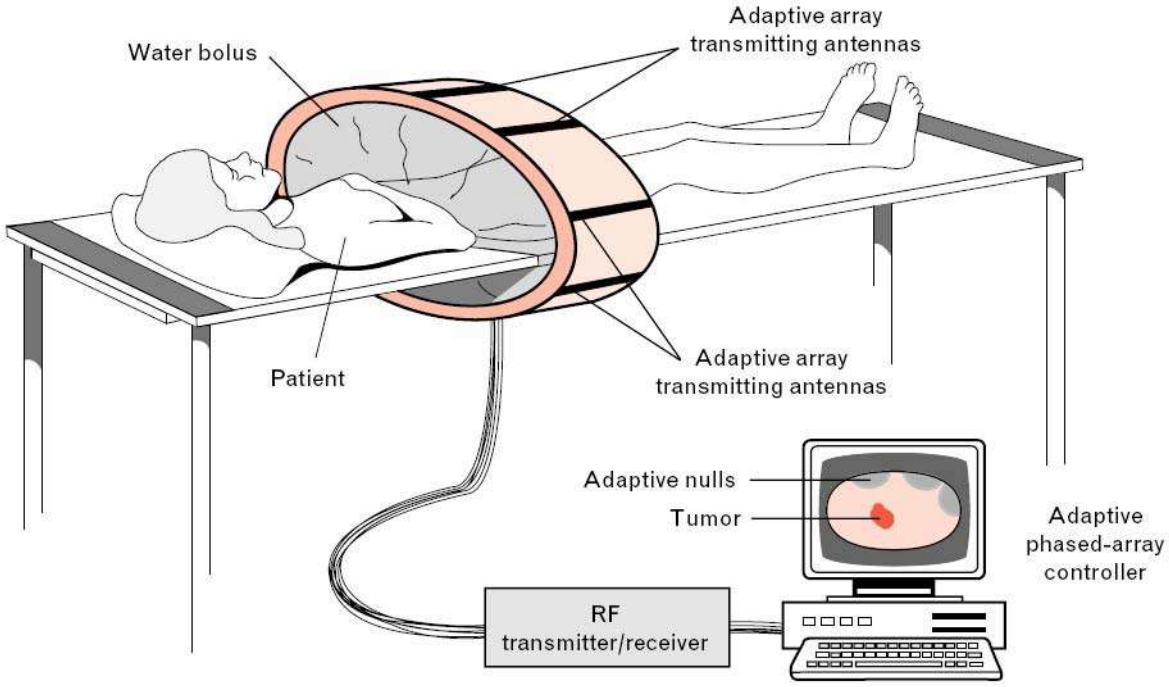


Fig 3: Hyperthermia treated with whole body

C.REGIONAL HYPERTHERMIA:

In regional hyperthermia a part of the body, such as an organ, limb, or body cavity (a hollow space within the body) is heated. In one approach, called *regional perfusion* or *isolation perfusion*, the blood supply to a part of the body is isolated from the rest of the circulation. The blood in that part of the body is pumped into a heating device and then pumped back into the area to heat it. Chemotherapy can be pumped in at the same time. To do this, surgery is needed to change the normal blood flow in the part of the body that is treated. Isolation perfusion is often is done under general anesthesia (drugs are used to make the patient sleep while it's done). Depending on the body part and how long the treatment will last, the temperature used may range from 104° F to 113° F. This technique is being studied as treatment for certain cancers in the arms or legs, such as sarcomas and melanomas.

A related technique can be used along with surgery to treat cancers in the peritoneum (the space in the body that contains the intestines and other digestive organs). During surgery, heated chemotherapy drugs are circulated through the peritoneal cavity.

1. OTHER REGIONAL HYPERTHERMIC TECHNIQUES:

Other regional approaches of clinical interest are under investigation for prostate cancer[61], preirradiated rectal cancer, and particularly use of partial body hyperthermia for peritoneal carcinosis (for ovarian cancer) in conjunction with chemotherapy (liposomal doxorubicin)[62].continous hyperthermia peritoneal perfusion is another technique used to treat cancers within the peritoneal cavity, including primary peritoneal mesothelioma and stomach cancer. During surgery, heated anticancer drugs flow from a warming

device through the peritoneal cavity. The peritoneal cavity temperature reaches 41-42^{o}C.

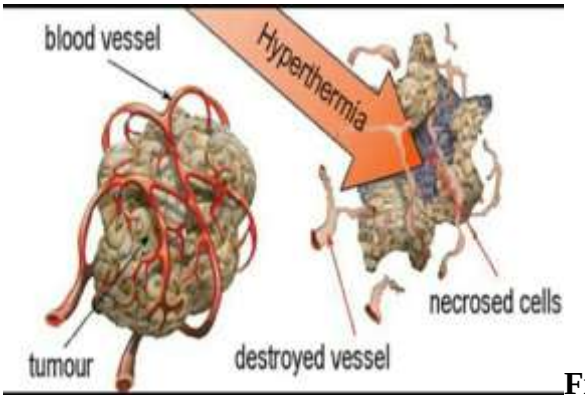


Fig4 :Destroying Tumour cel

TREATMENT PLANNING:

The control path of the HT treatment comprises many steps starting with amplitude and phase settings at multi-channel amplifier output stages and ending with desired temperature distributions in patient. Except for clinical follow-up, this control splits into two main parts: modeling of (1) electromagnetic and (2) thermo-physiological behavior. Electromagnetic
modeling comprises (CT- or MR-based) assignment of permittivity and conductivity distributions in patient, modelling of HT devices, and finally calculation of SAR distributions. Different numerical methods are used for SAR calculations. The two most popular are the finite elements (FE) and the finite-difference time domain (FDTD) methods.

Thermo-physiological modeling aims at solving numerically the bio-heat transfer equation under assumptions of known distributions of SAR, tissue heat conductivity and blood flow. The latter parameter is hardly appreciable and so the temperature prediction is, at the very least, controversial. This uncertainty notwithstanding, the temperature distribution remains clinically the most relevant predictor and therefore it is preferred in procedures of treatment optimization over SAR. In general, the calculated temperature distributions can be considered as underlying SAR distributions, which are smoothed at locally different strength. From the point of view of temperature distributions the very expense refinements in mapping of electrical tissue properties and SAR seem not to be justified. However, such refinements can be important, when relations between electrical properties and thermoregulatory perfusion changes will be once revealed. On the other hand, the refined models of RF devices generating heat have a large impact on the resulting temperature distributions (Fig. 5)

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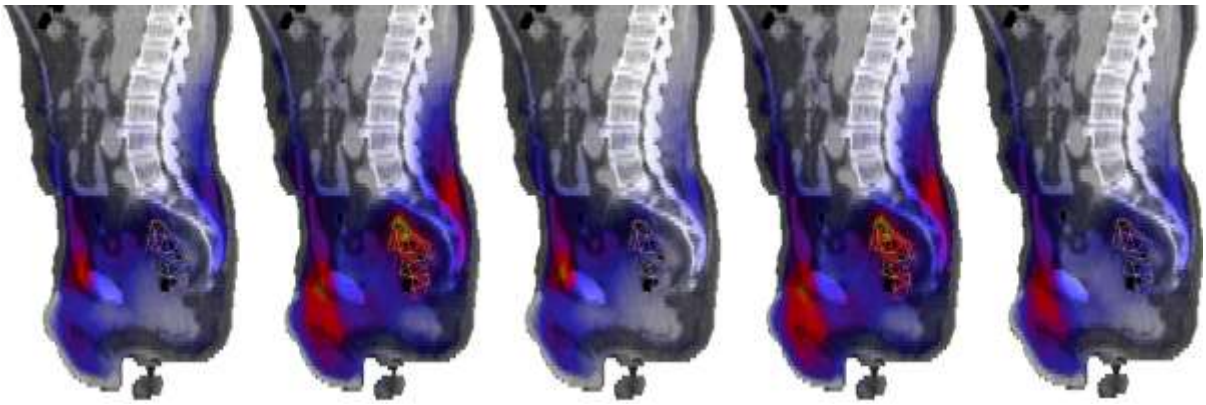

(a) (b) (c) (d) (e)

Fig. 5. Calculated temperature distributions for an HT treatment of a patient with a rectal cancer (indicated by a tetrahedral grid) in the 3-D Sigma-Eye applicator which was modeled without (a,b) and with the matching circuitry (c,d,e). For both applicator models temperature distributions were obtained for the synchronous (a,c) as well as for the optimized irradiation (b,d). The temperature distribution in (e) was obtained setting the optimum amplitude and phase values from (b) as control channel parameters for the applicator modeled with the matching circuitry. Note the deterioration of the temperature optimum in (e) with respect to (d), showing the importance of the modeling of the matching networks.

MALIGNANT HYPERTHERMIA:

Malignant hyperthermia is disease passed down through families that causes a fast rise in body temperature (Fever) and severe muscle contractions when the affected person gets general anesthesia. The only effective treatment for an MH crisis is the administration of dantrolene sodium,[64] a hydantoin derivative first developed as a muscle relaxant, Dr.Keith derivative first developed as a muscle relaxant, Dr.Keith ellis discovered that deantrolene acted on the intrinsic mechanism of skeletal muscle contraction and had no effect on cardiac or smooth muscle[65].The extract binds to the ryanodine receptor and interferes with the release of calcium into the myoplasm. This condition is not the same as hyperthermia that is due to medical emergencies such as heat stroke or infection .

CAUSES: Malignant hyperthermia is inherited .onlyb one parent has to carry the disease for a child to inherit the condition. It may occur with muscle diseases such as multiminicore myopathy and cental core disease(autosomal dominant).

SYMPTOMS:

- Bleeding
- Dark brown urine
- Muscle ache without an obvious cause, such as exercise or injury
- Muscle rigidity and stiffness
- Quite rise in body temperature to 105 degrees F or higher.

TREATMENT:

During an episode of malignant hyperthermia, wrapping the patient in cooling blanket can help reduce fever and risk of serious complications. Drugs such as dantrolene, lidocaine, or a beta-blocker drug can help with heart rhythm problems. To preserve kidney function during an episode ,you must get fluids through a vein and mouth , as well as certain medications.

Outlook : repeated episodes or untreated episodes can cause kidney failure. Untreated episodes can be fatal.

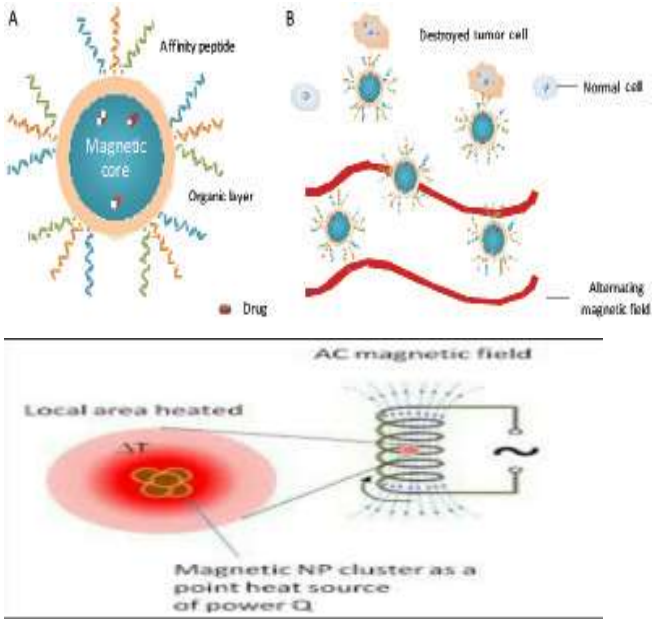

Fig 6: MALIGNANT HYPERTHERMIA

MEDICAL APPLICATIONS ON HYPERTHERMIA:

1. MEDICAL APPLICATIONS OF MAGNETIC NANOPARTICLES

Magnetic nanoparticles are used in a wide range of medical applications that include the following:

- A very special feature of magnetic nanoparticles is that they react to a magnetic force and this is used in applications such as bioseparation and drug targeting including cell sorting.
- These nanoparticles have become highly popular due to their use as heating mediators for cancer therapy and for magnetic resonance imaging (MRI).

A class of cationic magnetic nanoparticles, magnetite cationic liposomes can be used as carriers for the introduction of magnetite nanoparticles into target cells as their positively charged surface and negatively charged surface interact, also they can be used in hyperthermic treatments.

- Antibody-conjugated magnetoliposomes commonly known as AMLs are also used in hyperthermic treatments and enable tumor-specific contrast enhancement in MRI through systemic administration. The feature of manipulating cells labeled with magnetic nanoparticles using magnets finds application in tissue engineering. This is possible as magnetic nanoparticles are attracted to a high flux density.
- MCLs and magnetic force was used to build multilayered cell structures and a heterotypic layered three-dimensional coculture system.

It is anticipated that applying the unique features of these functionalized magnetic particles will enhance medical techniques.

1. X-rays and MRIs are truly a breakthrough achievement in the field of medicine; however, very soon it will be possible to regulate physiological and molecular changes taking place in the body. Dark brown oxide nanoparticles are anticipated to significantly improve the capabilities of presently available

medical imaging techniques.

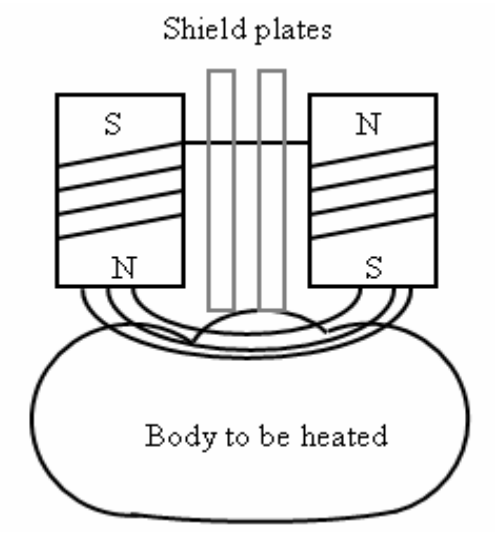

FIG.7 Inductive applicator for hyperthermia.

2. Application of hyperthermia to the treatment of human acute leukemia: purging human leukemic progenitor cells by heat.

The application of hyperthermia to the treatment of neoplastic disease has focused on solid tumors. Since the hyperthermic sensitivity of human acute leukemia cells is not known, we have studied the in vitro response of human leukemic progenitor cells (L-CFU) to hyperthermia using a quantitative assay system for L-CFU. Human L-CFU were found to be more sensitive than committed normal myeloid progenitor cells to hyperthermic killing (41 to 42 degrees C).

CHALLENGS AND FUTURE TRENDS : Most clinical hyperthermia systems operate by causing a target volume of tissue to be exposed to EM fields or ultrasound radiation. A structure is needed that is capable of transferring energy into biological tissue and getting the best approximation of the area to be treated by 3D distribution of SARs. The majority of the hyperthermia treatments are applied using external devices (applicators), employing energy transfer to the tissue.User needs require that the system be effective, safe, and robust. For a heating system to be effective, it must be able to produce final time and temperature histories that include a set of tumor temperatures that can be maintained for long enough times to result in clinically effective thermal doses without also producing unacceptable normal tissue temperatures.

TABLE 1

Summary of Major Hyperthermia Methods

HEATING APPROACH	ADVANTAGE	DISADVANTAGE	APPLICATION
Ultrasound	Good focus performance in tissue. No hot spots in fatty tissues. Heating possible to 5–10 cm depth with single transducer and up to 20 cm depth with multiple transducers.	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.

	Temperature is easy to measure and control.		
Radiofrequency	Simple instrumentation. No shield required. 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.	Treatment for large and superficial tumors in neck, limb, chest, brain, abdomen, etc.
Microwaves	Technology very advanced. Heating large volumes is possible. Specialized antennas for heating from body cavities have been developed. Multiple applicators, coherent or incoherent, can be used. Can avoid hot spots in the fatty tissues.	Heating not localized at depth; limited penetration at high frequencies. Temperature measurement is difficult and thermometry requires noninteracting probes. Possible health effects on personnel. Shielding of treatment rooms required, except at medically reserved frequencies (915 MHz).	For treatment of superficial tumors in breast, limb, prostate, and brain.

CONCLUSION :

Hyperthermia is a promising way to improve cancer treatment , but it is largely an experimental technique at this time . it requires special equipment, and a doctor and treatment team who are skilled in using it. Because of that , its offrered in only a few cancer treatment centers in the US and Europe.

Many clinical trials of hyperthermia are being done to better understand and improve this techniques.

For instance , the use of nanoparticals and induction heating of magnetic materials that are implanted into tumours are some new types of hyperthermia that are under study. And researchers continue to look at how hyperthermia is best us.

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