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Cancer Treatment with Hyperthermia

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1. Introduction

Broadly speaking, the term hyperthermia refers to either an abnormally high fever or the treatment of a disease by the induction of fever, as by the injection of a foreign protein or the application of heat. Hyperthermia may be defined more precisely as raising the temperature of a part of or the whole body above normal for a defined period of time. The extent of temperature elevation associated with hyperthermia is on the order of a few degrees above normal temperature (41–45°C) (Habash et al. 2006).

Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures, using external and internal heating devices. Hyperthermia is almost always used with other forms of cancer therapy such as radiation and/or chemotherapy. Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. It is proposed that by killing cancer cells and damaging proteins and structures within the cells, hyperthermia may shrink tumors making the cells more sensitive to radiation therapy (RT) and/or chemotherapy (ACS 2009).

In some cases if the elevated temperature is utilized as the stand alone technique, tissue temperature above 48 degree would be the objective.

hyperthermia induces almost reversible damage to cells and tissues, but as an adjunct it enhances radiation injury of tumor cells and chemotherapeutic efficacy. Because of the results that high temperature may produce in tissues, one can refer to use of temperatures >50°C as coagulation, 60 to 90°C as thermal ablation, >200°C as charring (Chichel A., et al. 2007). Hyperthermia, as a novel concept for cancer treatment has already entered clinical practice.

2. History

The clinical use of hyperthermia in the system of traditional medicine (Ayurveda) began in India around 3000 years ago. It formed part of a clinical protocol developed called "Panchakarma" that was used in curative and preventive medicine. Hippocrates (540-480 B.C) said that incurable disease is cured by heat, and demonstrated it using the hot sand in the summer. Semantically, hyperthermia comes from the Greek word hyper ("raise") and therme (heat).

Furthermore, Parmenides, Greek philosopher and physician said: "Give me the power to produce fever and I will cure any disease".
Cancer treatment by hyperthermia was first mentioned in ancient Rome by Cornelius Celsus Aulus, Roman encyclopedic doctor (25 BC - 50 AD), who noted that the first stages of cancer are extremely thermosensible.
In the Middle Ages hyperthermia was described by Leonidas - Nicolaus Leonicenus (1428-1524), professor of medicine in Padua. Fever was considered to be an agent of purification and detoxification of the body. After the Renaissance, there were reports of spontaneous tumor regression in patients with smallpox, influenza, tuberculosis and malaria, accompanied by fever.
Enthusiasm for applying heat diminished after 1537, when Ambroise Paré, military surgeon, has demonstrated that medical treatment by cauterization unacceptable consequences. In 1779 Dr Kizowitz described the effect of hyperthermia on malignant tumors caused by malaria.
As in modern ages, the literature on the use of hyperthermia, either as an adjunct to other treatments or as the primary mode of tumor eradication, goes back to the last century. The first paper on hyperthermia was published in 1886 (Bush W., 1886). It was claimed that the sarcoma on the face of a 43-year-old woman was cured when fever was caused by erysipelas. A decade later, (Westermark 1898) used circulating high temperature water for the treatment of an inoperable cancer of uterine cervix with positive results. Hyperthermia was already investigated for the treatment of malignancies more than a hundred years ago. Westermark reported on the use of localized, nonfever-producing heat treatments that resulted in the long-term remission of inoperable cancer of the cervix. Hot baths, electrocautery, and surgical diathermy were employed to locally raise tumor temperature. In the early twentieth century, both applied and basic research on hyperthermia was carried out; however, the heating methods and temperature measuring technologies were not sufficiently advanced at that time and positive clinical application of hyperthermia treatment was not accomplished.
The concept of using heat to treat cancer has been around for a long time, but early attempts to treat cancer with heat had mixed results. Several clinical trials were developed in the 1980s. Given the difficulties with hyperthermia delivery with the available technology and lack of widely applicable quality assurance guidelines enthusiasm for hyperthermia was about to disappear in the late 1980s. Despite little clinical success, research continued in the early 1990s (Hurwitz, 2010).
Worldwide interest in hyperthermia was initiated by the first international congress on hyperthermic oncology in Washington in 1975. Research on hyperthermia rose sharply during 1970's (Kim & Hahn 1979 and references therein). In the 1970's hyperthermia was investigated for the treatment of muscle invasive bladder cancer. More than ten years ago Matzkin performed an in vitro study where solely hyperthermia (43.8C) was used in the treatment of superficial transitional cell carcinoma (TCC) of the bladder . Results of several clinical trials are encouraging [Colombo et al]
In the United States, a hyperthermia group was formed in 1981 and the European Hyperthermia Institute was formed in 1983. In Japan, hyperthermia research started in 1978 and the Japanese Society of Hyperthermia Oncology was established in 1984.

3. Reasons for hyperthermia

The simplest curative application of heat that possess physiological basis (physiological hyperthermia) is treatment of aches, pains, strains, and sprains via application of

temperature below 41°C for approximately an hour and use physiological mechanisms of increasing blood flow and metabolic rates (Roemer RB. 1999).
For cancer treatment purposes, there are reports that malignant cells are more sensitive to heat than are their normal counterparts (Cavalieri, R.et al. and Levine, E.M), although that finding is not universal.
By now, several clinical studies have demonstrated the beneficial effect of regional hyperthermia (ZIB report 2008). Tumor cell environment, such as hypoxia, poor nutrition, and low pH, while detrimental to cell kill by ionizing radiation, is beneficial to heat therapy. Acidic environment of tumor confers resistance to radiation but favors cell kill due to heat.
The effect of hyperthermia depends on the temperature and exposure time. For example, it has been demonstrated that with a non-specific HT-applicator already a significant increase in local control (from 24% for RT alone versus 69% for RT plus HT) is achieved for metastatic lymph nodes, without additional toxicity.
Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients (Valdagni R., 1994).

4. Types of cancers

Cancer tumors located in various organs might be treated with different hyperthermia techniques. The chance of successful treatment depends on the stage of cancer development, application of specific technique, and response of patient's physiology to treatment. The cancer types already cured by hyperthermia are:
sarcoma, carcinoma , melanoma, head and neck, Brain
thyroid, lung, esophagus, breast,
kidney, bladder, liver, appendix, stomach,
pancreas, endometrial,
ovarian, prostate, cervix,
peritoneal lining. (mesothelioma).
rectum, appendix
By definition, the term "head and neck cancers" usually excludes tumors that occur in the eyes, in brain and in skin. The most frequently occurring cancers of the head and neck area are located in the oral cavity and the larynx. Worldwide, around 3-5% of patients suffering from cancer have tumors in the head and neck (H&N) region. (Paulides, M., 2007)

5. Physiological and biological phenomena in hyperthermia

First of all, it is noteworthy that there is no individual cellular target of hyperthermia, in contrast to the well known DNA damage after irradiation with x- , gamma or hadron.
In cellular level, reproductive death starts at 40 ^{0}C which is progressive with increasing time at the elevated temperature. Cells when heated to a temperature of 45 ^{0}C tend to undergo apoptosis or mitotic death process. Heat in the range of 42 ^{0}C to 45 ^{0}C, can also sensitize cells exposed to ionizing radiation or chemotherapy. The cells' sensitivity to heat shock is a function of their position in the cell cycle but heat-injured cells are capable of repairing sublethal and potentially lethal damage. (Hahn, G., 1974)
Inactivation curves showing duration of hyperthermic shock versus logarithm of surviving fraction have a shape similar to that for X-ray killing, i.e., a shoulder, followed by an approximately linear portion of the survival curve.

The results indicate that the cells in solid tumors that are most difficult to kill with conventional radio-therapy or chemotherapy may be those most readily eliminated by hyperthermia. Data indicate that elevated temperatures (39-43° C) increase the sensitivity of the cells to at least low-dose-rate X-irradiation and probably to some chemotherapeutic agents.
One of the important mechanisms of cell death is probably protein denaturation, observed at temperature above 40 ^{0}C, leading to changes in enzyme complexes for DNA synthesis and repair as well as alterations in structures like cytoskeleton and membranes. Heating cells at 42 ^{0}C for 10 minutes leads inhibition of DNA synthesis by 40 percent while, this figure amounts to 90 percent at 45 ^{0}C for 15 minutes. Heat can induce cell death in non-dividing cells by activation of various enzymes. Heat also affects cell membrane, a target not shared with ionizing radiation. Hypoxic cells, which are generally resistant to ionizing radiation, are sensitive to heat.
The cellular and molecular basis for this selective death of cancer cell has been studied. While inhibited RNA synthesis and mitosis arrest are reversible and nonselective results of hyperthermia, an increase in the number of lysosomes and lysosomal enzyme activity are selective effects in malignant cells. These heat-induced lysosomes are more labile in malignant cells and therefore result in increased destructive capacity. Furthermore, the microcirculation in most malignant tumors exhibits a decrease in blood flow or even complete vascular stasis in response to hyperthermia, which is in contrast to an increased flow capacity found in normal tissues. This, in combination with depression or complete inhibition of oxidative metabolism in tumour cells subjected to hyperthermia and unaltered anaerobic glycolysis, leads to accumulation of lactic acid and lower pH in the microenvironment of the malignant cell. (S. González-Moreno, et al, 2010)
Thus hyperthermia in the range of 42 ^{0}C-45 ^{0}C is good sensitizer of ionizing radiation. It is also shown to have synergistic effects with chemotherapy agents such as Bleomycin, Adriamycin and Platinol derivatives.
Increased perfusion due to warmer environment improves drug delivery to the tumor. It also ensures increased intracellular uptake of the drug as well as repair inhibition of DNA damage due to cytotoxic drugs. Combination of hyperthermia and chemotherapy also has shown decreased drug resistance. Interestingly an enhancement ratio of 23 was shown in cell lines when cell lines were treated with Melphalan and heat at 44 ^{0}C. (ACR 2008, ACR 2009).
Most of the biomolecules, especially regulatory proteins involved in cell growth and certain receptor molecules are largely influenced by hyperthermia. New insights from molecular biology have shown that a few minutes after hyperthermia, a special class of proteins are expressed into the cell, the so-called heat shock proteins (HSP). They protect the cell from further heating or subsequent thermal treatments and lead to an increase of cell survival after preheating, an effect called thermotolerance. Additionally, the activity of certain regulatory proteins is influenced by hyperthermia causes alterations in the cell cycle and can even induce apoptosis, the cell death driven by the cell regulatory system itself.
At tissue scale, primary malignant tumors have poor blood circulation, which makes them more vulnerable to changes in temperature (Habash 2006)
Cancer tissues accumulate lactic acid at an extremely increased glucose level, because cancer cells metabolize glucose to great extent into lactic acid, even in the presence of oxygen. This over-acidification makes the cancer cells more sensitive to hyperthermia. On the other hand, the normal cells are stabilized energetically by glucose in the presence of oxygen. Therefore,

in a temperature range between 41.9 and 42.5 °C, the cancer cells are destroyed or at least damaged. The normal tissues of the organism, however, are not affected.
HT kills cells itself, implicates radiotherapy by inducing reoxygenation, increases delivery of liposomally encapsulated drugs and macromolecules such as monoclonal antibodies or polymeric peptides, enhances cellular effects of chemotherapeutics and augments immune reactions against the tumor due to thermotolerance mediated by heat shock proteins (HSPs) (Mayerson, 2004).
The generation of free radicals by hyperthermia treatment (HT) in the membrane or cytoplasm of cancer cells, results in peroxidation of intracellular polyunsaturated fatty acids (PUFA), and is considered to be an important source of antitumor activity.

6. Thermal and electrical properties of tissue

	Relative Permitivity	Conductivity [S/m]
Muscle	62.8	0.72
Bone	14.6	0.068
Marrow	6.2	0.024
Skin	63.5	0.53
Blood	72.2	1.25
Tumor	74	0.89
Rest (high water content but includes some fat)	40	0.4

Table 1. Electrical properties of human tissues

	Mass Density [kg/m^3]	Thermal Conductivity [W/(m ^{0}C)]	Specific Heat [W/(kg ^{0}C)]
Muscle	1047	0.45	3550
Bone	1990	0.29	970
Marrow	1040	0.45	3550
Skin	1125	0.31	3000
Blood	1058	0.49	3550
Tumor	1047	0.55	3560
Rest (high water content but includes some fat)	1020	0.4	3200

Table 2. Thermal properties of human tissues.

7. Definition of radiofrequency, range of frequencies in hyperthermia

Designation	Frequency	Approximate wavelength
Radiofrequency (RF)	100 kHz	1000 m
	1 MHz	100 m
	10 MHz	10 m
	100 MHz	1 m
Microwave	1 GHz	10 cm
X-ray		

Table 3. Concise and approximate definition of frequency ranges in electromagnetic waves.

8. Treatment types: Local, regional, whole body

Depending on the organ bearing the cancerous tissue, stage of cancer development and method of energy delivery to patient's body, three kinds of hyperthermia techniques are recognized. This brings about various equipments and treatment works. These types are:

- Local hyperthermia
- Regional hyperthermia
- Whole-body hyperthermia

9. Local hyperthermia

Primary malignant tumors before the metastases stage are treated with local hyperthermia. Treatment is performed with superficial applicators of different shapes and kinds such as waveguide, spiral and current sheet placed on the surface of superficial tumors with an intervening layer called bolus. Energy sources could be RF, microwave, or ultrasound. When ultrasound is used, the technique is called high intensity focused ultrasound (HIFU). Heat is applied to a small area such as a tumor. The penetration depth depends on the frequency and size of the applicator; the clinical range is typically not more than 3–4 cm and the area is less than 50 cm^2. In local hyperthermia temperature rises to 42°C for one hour within a cancer tumor, hence the cancer cells will be destroyed.

There are several approaches to local hyperthermia including (ACS, 2009; NCI, 2004):

- External/Superficial: external applicator is used to deliver energy to the tumor below the skin
- Intraluminal or endocavitary: used to treat tumors within or near body cavities (e.g., rectum and esophagus) with placement of radiative probes inside the cavity.
- Interstitial: used to treat tumors deep within the body (e.g., brain tumors) with the use of anesthesia to place probes or needles into the tumor to deliver energy.

Candidates for local hyperthermia include chest wall recurrences, superficial malignant melanoma lesions, and lymph node metastases of head and neck tumors. Therapeutic depth is highly limited in regions with irregular surface, such as the head and neck (Habash et al, 2006)

10. Regional hyperthermia

For large, deeply seated, and inoperable tumors, regional hyperthermia is used. Cervical and bladder cancer are of this type. Another example is treatment of a part of the body, such as a limb, organ, or body cavity. In regional hyperthermia external applicators using microwave or radiofrequency energy are positioned around the body cavity or organ to be treated. (JJW Lagendijk et al, 1998).

A sub-group of regional hyperthermia is regional perfusion which is used to treat cancers in the arms and legs (e.g., melanoma) or cancers in some organs (e.g., liver and lung). Some of the patient's blood is removed, heated, and then pumped or perfused back into the limb or organ. Anticancer drugs are usually administered during this treatment.

Another kind of regional hyperthermia, hyperthermic intraperitoneal chemotherapy (HIPEC), also referred to as intraperitoneal hyperthermic chemotherapy (IPHC), has been proposed as an alternative for the treatment of cancers within the peritoneal cavity, including primary peritoneal mesothelioma and gastric cancer. The HIPEC is applied during surgery, via an open or closed abdominal approach. The heated chemolytic agent is infused into the peritoneal cavity, raising the temperature of the tissues within the cavity to 41-42^{0}C. (ACS 2009)

Whole Body Hyperthermia (WBH): WBH, achieved with either radiant heat or extracorporeal technologies, elevates the temperature of the entire body to at least 41 °C. There are various techniques of heating systemically. Immersion in temperature controlled hot water bath and radiant heat with U.V. are the usual techniques for whole body hyperthermia.

In radiant WBH, heat is externally applied to the whole body using hot water blankets, hot wax, inductive coils, or thermal chambers. The patient is sedated throughout the WBH procedure, which lasts less than four hours. The patient reaches target temperature within approximately 1 hour, is maintained at 41.8 °C for one hour, and experiences a one-hour cooling phase. During treatment, the esophageal, rectal, skin and ambient air temperatures are monitored at 10-minute intervals. Small probes may be inserted into the tumor under a local anesthetic to monitor the temperature of the affected tissue and surrounding tissue. Heart rate, respiratory rate, and cardiac rhythm are continuously monitored. Patients are returned to regular situation in patient rooms after hyperthermia and discharged after 20–24 hours of observation (Robins, et al., 1997; Green, 1991).

Extracorporeal WBH is achieved by reinfusion of extracorporeally heated blood. A circuit of blood is created outside the body by accessing an artery, usually the femoral artery, and creating an extracorporeal loop. The circulating blood is passed through a heating device, usually a water bath or hot air, and the heated blood is then reinjected into a major vein. The desired body temperature is adjusted and controlled by changing the volume flow of the warmed reinfused blood (Wiedemann, et al., 1994).

Extracorporeal hyperthermia treatments are conducted under general anesthesia. To counteract the activation of coagulation by the hemodialyzer, high-dose heparin is administered. An extracorporeal WBH treatment session typically lasts four hours. Target temperature is reached in two hours and is maintained for one hour, followed by a cooling period of one hour. Subsequently, the patient is infused with normal saline to maintain systolic blood pressure above 100 mm Hg. The patient is then monitored weekly for complications (Kerner, et al., 2002; Wiedemann, et al., 1994).

11. Treatment planning and simulation

Due to varying tumor location and geometry and different size and shape of patients, individual therapy planning is necessary. The first step of hyperthermia treatment planning is the generation of a patient model by segmentation of images from computerized tomography (CT) or magnetic resonance imaging (MRI) scans. In some cases, online parameter identification based on MRI is performed. A model of the applicator and this segmentation are used to calculate the power absorption (PA, [W/m3]) or specific absorption rate (SAR, [W/kg]) distribution in the patient by electromagnetic models. These EM models for treatment planning are commonly based on the finite-element (FE) method or finite-difference time-domain (FDTD) method. A temperature distribution in the patient can be calculated from the power absorption distribution by applying Pennes' bio-heat equation (PBHE), or more elaborate algorithms including the blood vessel network, i.e. discrete vasculature (DIVA) models, down to vessel sizes in the millimeter range. The main problems with these thermal methods are long time-requirements for the generation of a vessel network and the large, poorly-predictable, variations in thermal properties of tissues. The target in treatment planning is to heat a particular tumor and delivering at least 43°C to 90% of its volume for cumulative in multiple treatments for longer than 10 minutes corresponds to doubling of the probability for complete response and duration of response to hyperthermia and radiotherapy versus radiotherapy alone (Oleson et al. 1993).

The thermal iso-effect dose is an established quantity for assessing the therapeutic benefit of a treatment. As for now CEM 43°C T90 (cumulative equivalent minutes at a standard targeted treatment temperature of 43°C obtained within 90% of the tumour volume) appears to be the most useful dosimetric parameter in clinical research. Treatment planning based on the tumor cell survival has been proposed for thermoseed placement , but up to now rather ad hoc cost functional based on the temperature distribution or on the absorption rate density have been used for regional hyperthermia. (J. van der Zee et al 2007)

In local-regional hyperthermia therapy planning using RF as the heat source the therapeutically optimal antenna parameters for the applicator are determined for each patient. The specific absorption rate values are obtained by solving the Maxwell equations, and the temperature distribution is predicted by variants of the bio-heat transfer equation. Although this can be a demanding task, a planning tool greatly improves the medical treatment quality with a virtual experiment to model, simulate and optimize the therapy with high precision.[J Crezee et al. 2005]

12. Motivations for simulation

- Provide better heating through treatment preplanning.
- Optimize setups for treatment cases.
- Assist new applicator design in the future.

On the other hand, the perfusion depends on the temperature due to autoregulation capabilities of the tissue. Moreover, at least in abdominal hyperthermia, the systemic thermoresponse seems to play a significant role. Different perfusion models have been proposed, covering a broad spectrum of homogenized and discrete vascular models.

A mathematical model of the clinical system (radio frequency applicator with 8 antennas, water bolus, individual patient body) involves Maxwell's equations in inhomogeneous media and a so–called bio–heat transfer PDE describing the temperature distribution in the

human body. The electromagnetic field and the thermal phenomena need to be computed at a speed suitable for the clinical environment.
Finaly, in all treatment planning works an upper bound is imposed on the temperature: T <Tlim . Typical values for Tlim are 44 C for muscle, fat, and bone tissues, and 42 C for more sensitive organs such as bladder or intestine. (M. Weiser, 2008).

13. Instrumentation: Applicator, bolus, temperature measurement and monitoring

Hyperthermia can be applied by whole-body, external or interstitial/intracavitary techniques (applicators). External HT applicators use ultrasound (US) or electromagnetic (EM) waves to direct energy to the target region. US provides similar heating options as EM but results in more bone-pain complaints during treatment (Ben-Yosef et al. 1995).
In general, two types of probes are required in hyperthermia. One to deliver energy to the tissue, another to monitor the tissue temperature. The temperature in the tumor is measured by temperature sensors during the treatment. The temperature is then optimized continuously using automatic computer-controlled regulation of the applicator power output. Commercially Available Thermometer probes are :
Thermocouples
Thermistors
Non-perturbing probes
Thermistor sensor with high-resistance plastic leads containing graphite
Optical fibres
Liquid Crystal sensor
Birefringent sensor of LiNbO3
Fluorescent-type sensor made of two phosphorus
Semiconductor crystal, gallium-arsenide (GaAs) as a temperature sensor
Multichannel systems with non-perturbing multisensor probes
Multi-GaAs-sensors as a linear array with up to 8 sensor points in one probe
Multiple fluorescent phosphor sensors
Multiple thermistor sensors with high-resistance leads

Non-invasive thermometry

- Microwave multi-frequency Radiometry
- Computerized tomography (CT) for thermometry in vivo
- Nuclear Magnetic Resonance (NMR)
- Electrical impedance tomography (EIT)

The thermometers based on optical fibers offer the advantage of not possessing metallic components, and therefore they do not disturb the electromagnetic fields
The probe that delivers energy to the patient's body, usually referred to as applicator, ordinarily is in touch with skin. Every applicator includes a bolus which is placed on the patient's skin. For treatment, this bolus is filled with circulating water that can be heated as necessary. The bolus serves to physically couple the electromagnetic waves to the patient's body, and hence reduce the reflection and waste of energy.
Heating could be capacitative or inductive. Heating could be with external antennae or with interstitial and intracavitory probes. Intracellular heating with ferromagnetic material subjected to alternating magnetic field can also generate localized heating. RF at

8-12 MHz is useful for heating of the deep-seated tumor while, microwave heating at 434 MHz to 915 MHz is useful in surface tumors. Heating with ultrasound is also feasible. Mechanical ultrasonic waves delivered at 0.2-5MHz and can effectively heat a small volume at various depth.

In case of shallow tumors, the energy source is microwave 915 MHz generator. Commonly, it has eight channels, with phase and amplitude of each adjustable individually. Using a three-way splitter up to 24 antennas can be powered. The eight signals from the individual channels (each capable of delivering up to 50 watts) can be combined to provide a total output of up to 400 watts.

In order to deliver an optimal therapy, the phased array applicator needs to be controlled in such a way that the tumor is maximally heated without damaging healthy tissue by excessive temperatures. Pain and unpredictable heat deposition at tissue bone or tissue air cavity can be a limiting technological factor. Scanning transducers can overcome this difficulty. Ultrasound heating, unlike imaging has not gained popular use in the clinic.

14. Clinical techniques

Hyperthermia is mostly applied within a department of radiation oncology under the authority of a radiation oncologist and a medical physicist. It is always implemented as part of a multimodal, oncological treatment strategy, i.e., in combination with radiotherapy or chemotherapy. (Habash 2006).

In a hyperthermia clinic, the treatment starts with a comprehensive medical consultation with previous medical-imaging reports such as sonographics, X-rays, CTs, MRIs, nuclear medical images. If further examinations would be prescribed if necessary.

Depending on the indications, the hyperthermia treatment is given once or twice a week. Due to thermotolerance a general phenomenon pertaining to transient resistance to additional heat stress, it is impractical to apply two different HT sessions with an interval shorter than 48–72 hours, until the resistance decays to a negligible level**.** Total number of sessions depends on the tumor characteristics and varies between 5 and 10 per patient. chemotherapy is administered concurrently; radiation therapy must closely precede or follow the hyperthermia treatment by up to 120 minutes.

First, the patient is placed in a horizontal position. The temperature sensors are affixed to the skin above the tumor or inserted into the tissue through an implantable catheter. The number of temperature sensors used depends on the size of the tumor. The applicator, which is selected on the basis of the size and location of the tumor lesion, is held in the treatment position with the aid of either a support arm or holding straps.

On the day of main treatment, patients come at 8:00 to the hyperthermia-clinic with an empty stomach (on the day prior to the treatment, eating is permitted until 8:00 p.m. and drinking until midnight), a premedication (a sedative injection) is given in the morning before plus the attachment of an indwelling bladder catheter.

During an approximately 60-minute controlled infusion period, still at normal body temperature, the blood glucose level is increased by the three to four-fold of the initial value (by continuing the infusion during the TCHT main treatment, the blood glucose level attains a five to six-fold level of the initial value). Then, the body-warming-up process (hyperthermia) begins at approximately the same time as a moderate anaesthesia (neuroleptic analgesia at maintained spontaneous respiration; intratrachial intubation only if

neccessary) which acts over a time frame of approximately 6 hours. By means of infrared-A (short-wave part of the infrared spectrum) the body-core temperature is raised to 42.0°C (107.6 °F) within about 90 to 120 minutes. The chemotherapy is administered during the warming-up phase just before the body reaches 42.0°C

In the following so-called temperature-plateau-phase, a main body temperature of 42.0°C to 42.5°C is constantly maintained over 60 to 90 minutes. The cooling-off phase lasts for approximately another 90 to 120 minutes and uses the same monitoring measures as the warming-up and the plateau phase. An anti-emetic (a means to reduce vomiting) is added to the infusion during the last phase.

During the TCHT main treatment, lasting altogether approx. 8 hours, two doctors and two nurses are constantly at the patient's side(one doctor and a nurse continuously during the night and the next morning) then the patient will be transferred to the adjoining intensive care unit, an intensive care phase follows. The next morning at about midday the patient will be transferred by an accompanying doctor to the convenient private hospital to recover. For about 5 days the patients need infusions and medicines for recovery and initial daily blood sampling.

In a detailed report which you will take along, we recommend the follow-up checks as an outpatient later at the home town.

To make a general sense of external hyperthermia using RF, one could say the heat session is started by applying 80 W of total power with the power and phase control system (Bakker *et al* 2010), using the optimized phase and power settings from HTP.

Power is increased subsequently in steps of 30W, usually around one step per minute, till one of the tolerance limits is reached (40 ◦C in myelum indicative, 60Wkg−1 in myelum predicted by HTP, 43 ◦C in other tissues) or the occurrence of a hot spot indicated by the patient at a site without thermometry. Two phases of a treatment are defined for data analysis: (1) 'warm-up phase' and (2) 'plateau-phase', and the transition is assumed to be always after 15 min of heating.

The increased oxygen saturation in the blood results in a stabilization of the cardiac functions, the circulatory system, the respiratory system and the central nervous system. Some cytostatics act better in an acid environment, so that the efficacy of chemotherapy can be increased through overacidification of the tumor. Hyperthermia itself also increases the efficacy of some cytostatics. Some side effects of chemotherapy can be alleviated by relative hyperoxemia. On the basis of this complex interaction, an individually adapted chemotherapy in combination with the hyperthermia is highly effective and, in general, well tolerated.

External local hyperthermia is utilized or heating of small areas (usually up to 50 cm2) to treat tumors in or just below the skin up to 4 cm. This can be used alone or in combination with radiation therapy for the treatment of patients with primary or metastatic cutaneous or subcutaneous superficial tumors (such as superficial recurrent melanoma, chest wall recurrence of breast cancer, and cervical lymph node metastases from head and neck cancer). Heat is usually applied using high-frequency energy waves generated from a source outside the body (such as a microwave or ultrasound source).

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 (1) gastrointestinal (esophagus, rectum), (2) gynecological (vagina, cervix, and uterus), (3) genitourinary (prostate, bladder), and (4) pulmonary (trachea, bronchus). Very

localized heating is possible with this technique by inserting an endotract electrode into lumens of the human body to deliver energy and heat the area directly.

The transient phase of heat distribution in patient's body takes about 15 minutes, while the duration of a single treatment session is about two hours. For this reason, usually only the steady state of the temperature distribution is optimized, which results in a significantly simpler optimization task.

Hyperthermia is most effective when the area being treated is kept within an exact temperature range for a defined period of time without affecting nearby tissues. This is challenging since not all body tissues respond in the same way to heat. Small thermometers on the ends of probes are placed in the treatment areas to monitor the desired temperature. Magnetic resonance imaging (MRI) is proposed as a replacement of the probes to monitor the temperature (ACS, 2009).

The following measures are taken in order to intensively monitor all the body functions. Two peripheral venous accesses in the form of flexible soft-tip catheters are attached for infusions, intravenous injections and blood sampling. The painless localization of the thermometric probes (rectal, axillary, as well as on the skin of the stomach and the back), of the pulse oxymeter (on the right middle finger) and of the ECG miniature adhesive electrodes complete the intensive medical monitoring. During the whole treatment time, the ECG and oxygen saturation are very closely observed and all the relevant parameters are monitored by means of blood samples every 15 minutes. Continuous blood pressure measurements as well as regular blood-gas analysis are monitored. In this way possible deviations are recognised and corrected early. Serious disturbances can thus be averted to the greatest possible extent.

15. Case studies

In a study involving 109 patients with superficial tumors, patients mostly suffering from breast wall recurrence due to mammary carcinoma, the enhancement effect of hyperthermia in combination with radiation therapy was demonstrated. Previously irradiated patients who underwent a second round of radiation therapy in conjunction with hyperthermia responded significantly better to this therapy. Complete remission was achieved in 68% of those treated with hyperthermia plus radiation while in the control group who did not receive hyperthermia, complete remission was observed in only 24% of the patients. (Jones, E.2005)

The effectiveness of hyperthermia treatment in cases of advanced head and neck tumors has been confirmed (R. Valdagni and M. Amichetti 1994). With radiation therapy alone, complete remission was achieved in 41% of patients, while the combination of radiation therapy and hyperthermia increased the remission rate to 83%. In addition, the 5-year survival rate for these patients was increased from zero to 53% from the addition of hyperthermia to radiation therapy.

There are nearly 24 randomized studies reported to which 18 have reported a positive benefit in combining hyperthermia with radiation. Patients with cervical nodes were randomized to radiation alone to a dose of 64-70 Gy and radiation with hyperthermia. Hyperthermia was delivered twice a week. The initial response was reported to have improved from 41% to 83% with a 5 year overall local control increasing from 245 to 69% and survival from none to 53%9. Addition of hyperthermia to radiation in cancer of cervix was reported to have improved outcome as compared to radiation (N. G. Huilgol)

Bladder cancer at various stages was studied for 358 patients from 1990 to 1996. Patients were divided to two groups. One group underwent radiotherapy (median total dose 65 Gy) alone (n=176) another group radiotherapy plus hyperthermia (n=182). Complete-response rates were 39% after radiotherapy and 55% after radiotherapy plus hyperthermia. The duration of local control was significantly longer with radiotherapy plus hyperthermia than with radiotherapy alone. The 3-year overall survival was 27% in the radiotherapy group and 51% in the radiotherapy plus hyperthermia group (Van der Zee 2000).

For ovarian cancer, in vitro studies have shown that hyperthermia produces a dose-enhancement effect (i.e. a thermal enhancement ratio of approximately 3 for a 60 min heat exposure) besides, it is shown that hyperthermia can overcome acquired drug resistance . (A.M.Westerman 2001)

Around 70% of all initial responders to chemotherapy make no improvement and subsequently require additional therapy. The classic treatment includes aggressive tumor reductive surgery (TRS) followed by platinum based combination chemotherapy, using cisplatin or carboplatin combined with a taxane. As an adjunct to traditional therapy, hyperthermia has been shown to enhance cisplatin cytotoxicity. Mild hyperthermia (39–43°C) has successfully been utilized in combination with chemotherapy to increase cellular sensitivity to anticancer drugs mainly using an intraperitoneal approach. The interaction between heat and chemotherapeutic agents results in increased drug uptake by accelerating the primary step in a drug's efficacy and increasing the intracellular drug concentration. Therefore, the combination of hyperthermia and anti-cancer drugs may reduce the required effective dose of the anti-cancer drug, and it could enhance the response rates in ovarian cancer cells. (Amber P. et al, 2007)

Local recurrence rates of breast cancer after mastectomy alone have been reported as high as 45%. This high rate of failure can be reduced to 2–15% with the addition of postmastectomy radiation therapy (PMRT) and usually chemotherapy as well, with a corresponding improvement in overall survival. With its radiosensitizing properties, hyperthermia presumably lowers the radiation dose needed to achieve durable local control, which in turn has potential implications for decreased long-term toxicities in patients with a prior history of radiotherapy. The addition of concurrent chemotherapy to hyperthermia and radiation therapy, constituting thermochemoradiotherapy (ThChRT)), has been evaluated in phase I/II trials by several researchers and found to be well-tolerated, with moderate success. (Timothy M. Zagar et al 2010)

16. Side effects

The possible side effects of hyperthermia depend of the technique being used and the part of the body being treated. Pain, thermal burns or blisters are the limiting adverse events of the techniques. Fewer side effects are observed with improvement in technology along with better skills and improved technology (ACS, 2009; ECRI, 2007). Post surgical site may be more susceptible to heat due to poorly vascularised state. Skin and subcutaneous tissues are generally susceptible to increased power deposition when heated with microwave and radiofrequency waves. Thermal burns which are superficial and generally heal quickly are seen in 2-15% of the patients (N. G. Huilgol)

In case of thermochemotherapy (TCHT) during the first days after the main treatment, the occurrence of fever up to 39 °C can be observed as an expression of a strong

immunostimulation and is desirable in most cases. At this time, though, exhaustion, weakness,
Nausea, vomiting, headaches, diarrhoea and herpes labialis (blisters on the lips) can also occur.
Cases requiring treatment are, however, observed in less than 3 % of the therapies.
In rare single cases after TCHT treatment, an increased amount of oncolytical products can lead to an overstrain of the excretory mechanism (liver, kidney). As a consequence, temporary jaundice (icterus) as well as an increase of the liver and kidney values may occur.
Although the side effects of most of the cytostatics are milder than those of conventional chemotherapy, toxic effects of isolated cytostatics caused by the TCHT are observed in very few cases. Temporary functional disturbances of the peripheral nerves can, though, occur with temporary strength reductions.
During the TCHT main treatment, a moderate anaesthesia is given. The patient is unable to drive for at least three days after the main treatment. In the following days, due to various reasons (e.g. after-effects of the chemotherapy or additional medications), reaction times can be deteriorated and, therefore, driving ability is considerably limited. Most of these side effects are temporary.

17. Engineering aspects of hyperthermia: Modeling, computation of temperature distribution, computer applications

Energy absorption in cancerous tissue provides heat required for temperature increase. Predominantly, electromagnetic waves in various frequency ranges are utilized. Thus, Maxwell's equations must be solved for the specific geometry with estimated electrical properties at the given anatomy. This computation process leads to SAR (Specific Absorption Rate) in Watts per unit mass of tissue. Then heat transfer equation must be solved to reproduce the temperature distribution in cancerous tissue and the adjacent healthy tissue. In contrast to RF ablation and focused ultrasound therapies, electrical and thermal properties of tissue do not change significantly over 37 - 45 temperature range. For this reason, these values are simply taken as constants depending only on tissue type.
Due to irregular geometry, modeling errors for computing the electrical field exists. Thus, even accurate solution of Maxwell's equations will not provide the actual electrical field. As a reliable tool, MRI can be used for monitoring the temperature distribution and identification of the applicator parameters. The 3D voxel data can be obtained approximately every other minute from proton resonance frequency shifts.
When using RF as the energy source, a time-harmonic electrical interference field is generated by a phased array of antennas which can be controlled individually by variations in amplitude and phase of each source.(M. Werser 2008).
A system for local hyperthermia consists of a generator, control computer applicator, and a scheme to measure temperature in the tumor. The therapy system is controlled automatically by the computer, which can be operated either via a touchscreen or by means of a mouse and keyboard.
To produce a visualization of the model from the patient's anatomy, the computer in clinic is equipped with GPU (Graphical Processing Unit). The GPU is the heart of a graphics card. Due to the application in multibillion game market, GPUs have quickly evolved into powerful devices available at a low price. This makes them attractive not only for graphics of video games, but also for scientific computing. GPUs are so fast because they are inherently parallel: while CPUs have 2 to 4 cores, GPUs have up to 128 arithmetic units.

18. Application of nanoparticles in hyperthermia

The difficulty in limiting heating close to the tumor region without damaging the healthy tissue is a technical challenge in hyperthermia. The use of magnetic nanoparticles can overcome the difficulty in spatial adjusting of power absorption by cancerous tissue. Application of magnetic materials in hyperthermia was first proposed in 1957 (Gilchrist R. K., et al. 1957)

Magnetic induction hyperthermia is a technique for destroying cancer cells with the use of a magnetic field. The temperature of the cancer tissue can be raised in the range of 42–46 C, by indirect heating produced by various magnetic materials introduced into the tumor. Depending on increase in temperature, cell damage (necrosis) or even its direct destruction (thermoablation) may be promoted.

A large number of magnetic materials for magnetic induction hyperthermia have been developed. The major part of ferro-, ferri-, as well as superparamagnetic materials are suitable for this specific application. An important requirement of all these materials is biocompatibility. MgO-Fe is common material of choice in recent research.

The heating capacity depends on the material properties, such as magnetocrystalline anisotropy, particles size and microstructure. To enable them to penetrate into smallest part of every tissue or even into cancer cell, magnetic material is made with nanometer size, called magnetic nanoparticle (MNP).

Cancerous cells typically have diameters of 10 to 100 micrometers. This has produced the motivation to use MNP to penetrate into a cell.

The particles used in hyperthermia exhibit ferro- or ferrimagnetic properties. These particles have permanent magnetic orientations or moments and some kinds display magnetism even in the absence of an applied magnetic field (Pankhurst *et al*.).

Magnetic nanoparticles are designed to selectively be absorbed in tumor. Once in the tumor, they agitate under an alternating magnetic field and generate heat within tumor. Heat generation is due to different magnetic loss processes such as moment relaxation (Ne´ el), mechanical rotation, (Brown) or domain wall displacements), leading to the destruction of the tumor, whereas most of the normal tissue remains relatively unaffected.

Particles with diameters of 10 nanometers or less typically demonstrate superparamagnetic properties. The magnetic moments of superparamagnetic nanoparticles are randomly reoriented by the thermal energy of their environment and do not display magnetism in the absence of a magnetic field. Unlike ferro- and ferrimagnetic materials, they do not aggregate after exposure to an external magnetic field (Berry and Curtis). Aggregation can hinder the body's efforts to remove the nanoparticles. Therefore, superparamagnetic nanoparticles are ideal candidates for hyperthermia cancer treatment.

Nanoparticles can also effectively cross the blood-brain barrier, an essential step in treating brain tumors (Koziara et al.). Finally, nanoparticles can be coupled with viruses (20-450 nm), proteins (5-50 nm), and genes (10-100 nm long) (Pankhurst et al.).

In practice, MNP is introduced into patient's body by injecting a fluid containing magnetic nanoparticles. This technique is called Magnetic fluid hyperthermia (MFH). When placed in an alternating magnetic field with frequencies in tens to hundreds MHz, MNP begin to agitate and produce enough heat inside the tumor. In this technique, only the magnetic nanoparticles absorb the magnetic field. No heat generation in healthy tissue is the advantage of this technique over other hyperthermia techniques such as laser, microwave, and ultrasound.

Magnetic nanoparticles are evenly dispersed in water or a hydrocarbon fluid. Small size of dissolved particles leads to little or no precipitation due to gravitational forces. For medical applications, the biocompatibility of both the fluid and nanoparticles must be considered. The fluid must have a neutral pH and physiological salinity. In addition, the magnetic material should not be toxic. The established biocompatibility of magnetite (Fe3O4) makes it a common choice.

The heating ability of MNPs is expressed by the specific absorption rate (SAR), which is equal to the power loss per material mass. Generally, it is advantageous to achieve the temperature enhancement needed for any application with as low as possible MNPs concentration. For a specific nanoparticle system, SAR is directly related to the applied field amplitude and frequency as well as to geometrical (size, shape) and structural features of the particle. Although various magnetic nanomaterials present high SAR values, the demand for low MNPs concentration and biocompatibility issues restricts significantly materials choice. An alternate route towards larger SAR values is expected to be the enhancement of magnetic moment per particle, e.g. the use of Fe particles coated by a biocompatible shell such as MgO , instead of iron oxides, besides the higher magnetization, it also provides a satisfactory solution to the problem of chemical stability and biocompatibility. Water soluble Fe/MgO nanoparticle is the basis of magnetic hyperthermia. The use of zero-valence iron particles, instead of iron oxides, provides improved magnetization values while the MgO coating serves as a satisfactory solution for the achievement of chemical stability and biocompatibility. The non-toxicity of magnesium-based materials, their corrosion resistance and antimicrobial action are fields of intense research. (A. Chalkidou, et al. 2011) and (O. Bretcanu, et al, 2006)

19. Hyperthermia in combination with other modalities

As an adjunct to traditional cancer therapy, hyperthermia has been shown to enhance cytotoxicity of chemotherapy agents. Since adequate heating of the whole tumor volume is difficult except for superficially located small tumors, and in general the reported response duration is short, the use of hyperthermia alone is not recommended (van der Zee, et al., 2008). Mild hyperthermia (39–43°C) has successfully been utilized in combination with chemotherapy to increase cellular sensitivity to anticancer drugs mainly using an intraperitoneal approach. The interaction between heat and chemotherapeutic agents results in increased drug uptake by accelerating the primary step in a drug's efficacy and increasing the intracellular drug concentration. Therefore, the combination of hyperthermia and anti-cancer drugs may reduce the required effective dose of the anti-cancer drug, and it could enhance the response rates in cancer cells. The results of combined application of chemotherapy and hyperthermia has been satisfactory .

The thermo-chemotherapy (TCHT) is a combined modality treatment with high tolerance for malignant tumors of the mammary gland, of the whole gastric intestinal tract (specially pancreatic cancer), of the lungs, of the urogenital tract (specially ovarian-cancer), of the skin, bones and soft-tissues as well as oral and neck advanced malignant tumors (specially node metastasis). In principle, adenocarcinoma and squamous epithelium carcinoma with metastasis (as well bone metastasis) or without metastasis, osteo sarcoma and soft-tissue sarcoma of nearly all localisations, the malignant melanoma and non-Hodgkin lymphoma and also pleural malignant mesothelioma can be treated. The TCHT main treatment, which

lasts several hours, is followed by approximately 24 hours of intensive care treatment in the specially equipped hyperthermia-clinic.
The treatment itself is based on a controlled interaction between whole-body hyperthermia (body warming-up), induced hyperglycaemia (increasing of the blood glucose level), relative hyperoxemia (oxygen enrichment of the blood) and pre-arranged with the patient modified chemotherapy. Thanks to this multistep therapy, one has the chance to positively influence the course of the illness - even when tumors have not previously responded to radiotherapy, to cytostatics or to hormones.

20. A brief overview of important softwares

In order to permit a patient–specific treatment planning, a special software system (HyperPlan) has been developed.
COMSOL is a general purpose software to compute electromagnetic fields interaction with matter.
SEMCAD X takes the segmentation and a CAD implementation of applicators as input and tissue and material properties are assigned to the solid models. With a proper set-up, the electric fields for each antenna are calculated using the electromagnetic solver of SEMCAD X.
The position of tumor in the patient's body along with neighboring organs and tissues can be reconstructed by Ansoft Human-Body Model. The accuracy of this software is at millimeter level. There are more than 300 objects defined in this model including bones, muscles and organs. Frequency-dependent material parameters are included as well.

21. Prospects

- Heating deep seated tumors effectively still remains an unsolved technical problem.
- Hyperthermia may find additional indications in gene therapy, stem cell purging, drug targeting with heat sensitive liposomes and potentiation of immunity in HIV.
- The reliability of the mathematical optimization depends on the accuracy of the models describing the physical situation. In particular the physiological parameters are individually varying to a significant amount, such that a priori models are subject to significant modelling errors.
- The physical processes of field interference and heat distribution inside the very heterogeneous human body is too complex to be optimized manually. Thus, optimization algorithms are required for therapy planning,

22. Conclusion

Although basically an old and historic approach for treatment of cancer, hyperthermia is not a well-known modality among patients and medical experts. On the other hand, it has proved a very successful therapy method in combination with radiation therapy and / or chemotherapy. The precise mechanism of cancer development and destruction is not known; especially the response of different patients at similar situation is quite unpredictable. At clinical stage, the mathematics behind the treatment planning is difficult to implement for complicated geometry of tumor. The heat transfer and SAR parameters are not identical among patients. Up to the best knowledge of authors of this chapter, these parameters might not be measured with a proper precision, especially at clinical practice.

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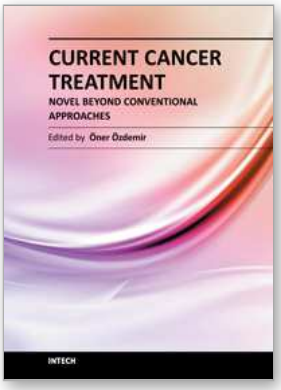

Current Cancer Treatment - Novel Beyond Conventional Approaches

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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