

## Hyperthermia versus Oncothermia: cellular effects in cancer therapy

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## ***Abstract***

Hyperthermia means overheating of the living object completely or partly. The fact the hyperthermia is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the focusing of the heat-effect. The idea of oncothermia solves the selective deep action on nearly cellular resolution.

We would like to demonstrate the perspectives of oncothermia, as a highly specialized hyperthermia in clinical oncology. Our aim is to prove the ability of oncothermia to be a candidate to become a widely accepted modality of the standard cancer-care. We would like to show the proofs and the challenges of the hyperthermia and oncothermia applications to provide the presently available data and summarize the knowledge in the topic. Like many early-stage therapies, oncothermia lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

## ***Introduction***

In oncology, the term “hyperthermia” refers to the treatment of malignant diseases by administering heat in various ways. Hyperthermia is usually applied as an adjunct to an already established treatment modality, where tumour temperatures in the range of 40–46°C are aspired. Interstitial hyperthermia and whole-body hyperthermia are still under clinical investigation, and a few positive comparative trials have already been completed. In parallel to clinical research, several aspects of heat action have been examined in numerous pre-clinical studies [1, 2, 3].

The traditional hyperthermia is controlled the only single thermodynamic intensive parameter, with the temperature. Oncothermia, which is a “spin-off” form of the hyperthermia, is based on the paradigm of the energy-dose control, replacing the single temperature concept [4]. With this approach oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which can not regarded as dose (the temperature does not depend on the volume or mass), oncothermia uses the energy (kJ/kg [=Gy]), like the radiation oncology uses the same (Gy) to characterize the dosing of the treatment [5].

For further information read the longer version of this paper which readable on-line: <http://www.hindawi.com/journals/ecam/aip/672873/> and accepted for publication of the special issue of the Evidence-Based Complementary and Alternative Medicine (Translational Research in Complementary and Alternative Medicine).[6]

## ***The concept of hyperthermia***

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. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumour and surrounding tissues is monitored throughout the hyperthermia procedure. The goal is to keep local temperatures under 44°C to avoid damage to surrounding tissues, and the whole body temperatures under 42°C, which is the upper limit compatible with life [5].

## ***Cellular mechanisms induced by hyperthermia***

The cellular effect of hyperthermia is more complicated [7, 8]. Briefly, hyperthermia may kill or weaken tumor cells, and is controlled to limit effects on healthy cells. Tumor cells, with a disorganized and compact vascular structure, have difficulty dissipating heat. Hyperthermia may therefore cause cancerous cells to undergo apoptosis in direct response to applied heat, while healthy tissues can more easily maintain a normal temperature. Even if the cancerous cells do not die outright, they may become more susceptible to ionizing radiation therapy or to certain chemotherapy drugs, which may allow such therapy to be given in smaller doses. Intense heating will cause denaturation and coagulation of cellular proteins, rapidly killing cells within the targeted tissue. A mild heat treatment combined with other stresses (excitation of the appropriate signal-pathways) can cause cell death by apoptosis.

The potential importance of the hyperthermia for cancer treatment has been highlighted by Coffey et al. [7, 8]. Specifically the review addresses four topics: (1) hyperthermia induced cell killing, (2) vascular, (3) cellular and intracellular mechanisms of thermal effects in the hyperthermia temperature range and (4) effects on proteins that contribute to resistance to other stresses, for example, DNA damage.

(1) Hyperthermia induced cell killing: It has been long recognized that hyperthermia in the 40–47°C temperature range kills cells in a reproducible time and temperature dependent manner. In the hyperthermic region there are three cellular responses for thermal therapy: cytotoxicity, radiosensitization and thermotolerance [9, 10]. The intensity of cell death in hyperthermia is showed cell cycle dependence. Both S- and M-phase cells undergo a “slow mode of cell death” after hyperthermia. Cells during G1-phase may follow a “rapid mode of death” immediately after hyperthermia [11, 12, 13].

(2) Vascular: With higher heat temperatures there is a corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability [14, 15]. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death [16]. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases [17, 18].

(3) Cellular and intracellular mechanisms of thermal effects in the hyperthermia - Cell metabolism: hypoxia, pH, ATP and its consequences: Summarizing the relevant data, it can be stated that tumour temperatures >42.5°C and appropriate heating can reduce both intracellular and extracellular pH, which may further sensitize tumour cells to hyperthermia in the sense of a positive feedback mechanism [19]. Relevant pathogenic mechanisms leading to an intensified acidosis upon heat treatment (which is reversible after hyperthermia) are:

1. an increased glycolytic rate with accumulation of lactic acid,
2. an intensified ATP-hydrolysis,
3. an increased ketogenesis with accumulation of acetoacetic acid and b-hydroxybutyric acid,
4. an increase in CO<sub>2</sub> partial pressures,
5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
6. an inhibition of the Na<sup>+</sup>/H<sup>+</sup>-antiporter in the cell membrane [20, 21].

The ATP decline observed upon heat treatment is mostly due to

1. an increased ATP turnover rate (i.e. intensified ATP hydrolysis). As a result of an increased ATP degradation, an accumulation of purine catabolites has to be expected together with a formation of H<sup>+</sup> ions and reactive oxygen species at several stages during degradation to the final product uric acid,
2. a poorer ATP yield as a consequence of a shift from oxidative glucose breakdown to glycolysis [19].

(4) Effects on proteins that contribute to resistance to other stresses, for example, DNA damage: At higher temperatures, inhibition of HSP-synthesis occurs above a distinct threshold temperature. In general, the temperature, respectively, thermal dose at which HSP synthesis is inhibited in a given experimental system varies between different cell types, but the respective threshold can be lowered when further (proapoptotic) stimuli are added. As lack of HSP-synthesis is associated with exponential cell death, it is generally accepted that HSPs prevent cells from lethal thermal damage. Recently, an additional role has been ascribed to HSPs which should be importance in hyperthermia as activators of the immune system [22, 23, 24, 25].

### ***Problems with hyperthermia***

The high energy application could cause controversies: the high temperature burns the malignant cells but it's missing selectivity. The healthy cells are damaged also and the hyperthermia starts unwanted physiological reactions as well as enlarged dissemination possibility. These conditions make the hyperthermia effect not controlled.

### ***Change of paradigm – the concept of oncothermia***

Oncothermia technology heats non-equally; concentrating the absorbed energy to the intercellular

electrolytes [26]. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis [27].

Oncothermia works with much less forwarded energy, by focusing energy directly on the malignant tissue using its impedance selectivity even by cellular resolution. This effect is based on the low impedance of the tumor, due to its metabolism, which is higher than that of its healthy counterpart's [28]. Based on microscopic effects, there not only the heating makes the effect, but the electric field itself has a strong synergy with this, having significantly larger cell killing in malignancy at 38oC, than the conventional hyperthermia has on 42oC. The process is selective. The radiofrequency current is choosing the "easiest" path to flow, and due to the high ionic concentration of the near-neighborhood of malignant cells, the current will be densest at the tumor cells. The experimental results well support this idea. In the case of healthy cells the load is equal for all the cells, no difference between the treated and control samples. When we gain the metabolism (immortalized cells) but not yet malignant acceleration, the effect is selectively higher but not significant. However, when the malignancy is present, the cellular growth is aggressive, the selection became effective, and kills the tumor cells without affecting the healthy ones in the coculture.

This electric field effect well demonstrates, that the average kinetic energy (temperature) has not decisional effect. The main action is the targeted energy-delivery, which could be done on such low average energy as the standard healthy body temperature.

### ***Cellular mechanisms induced by oncothermia***

Clinical oncothermia can induce the following cellular mechanisms:

(1) Oncothermia promotes the programmed cell-deaths of tumor: Detecting the double strains of DN and measuring the enzymatic labeled strain-breaks of DNA the apoptosis is highly likely in oncothermia [29]. Consequently the main effect in oncothermia is the apoptosis contrary to the conventional hyperthermia, which operates mainly by necrosis. Investigating the apoptosis by various methods (morphology, beta-catenin relocation, p53 expression, Connexin 43, Tunel, DNA-laddering etc.) the effects are indicating the same apoptotic process. This process is non-toxic (no inflammatory reactions afterwards) and promotes the immune reactions and not makes processes against those.

(2) Oncothermia limits the dissemination of malignant cell: Oncothermia blocks the tumor cell dissemination, avoid their motility due to the lazy connections to the tumor. Oncothermia makes it by the reestablishing the cellular connections, which is also great success to save the life. The built up connections could force not only the sticking together, but makes bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells. These are high efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart. It also produces higher concentration of HSPs in the outer membrane and in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis.

### ***Legal note***

According to European Medical Device Directive (MDD) oncothermia is certified by TUV, Munich by medical CE certificate; (both safety and efficacy are certified). All the devices are manufactured according to the ISO 9001 and ISO 13458.

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