"Quo vadis" oncologic hyperthermia?

Prof. Dr. Andras Szasz[1]
(1) Biotechnics Department, St. Istvan University, 2100-Godollo, Pater K. u. 1., Hungary
(Szasz.Andras@gek.szie.hu)

This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

“Quo vadis” oncologic hyperthermia?

Abstract

Hyperthermia was the very first first oncotherapy in human medicine based directly on sacral and philosophical roots in ancient cultures. The discovery of electromagnetism gave new hopes a century ago, however until up to now it has been suffering from lack of wide applications. Oncological hyperthermia struggles with multiple technical and medical problems which are far from the complete solution. Technically the deepheating, the precise focusing, the technical control and repeatability are challenging. The missing medical explanation of the phenomena, the missing acceptable and measurable dose, and the contra-feedback of physiology mechanisms block its acceptance. Multiple, most promising results and studies are mixed together with some negatives and controversial consequences, causing huge fluctuations of its applications. There are positive and negative “believers” of the method, but the decisional facts are missing. A new way gives shape to the development: heating in nano-range, which could solve most of the open problems in oncological hyperthermia.

Keywords: hyperthermia, oncology, nano-heating, focusing, selection, dose

Introduction

Hyperthermia is an ancient treatment. Hyperthermia means overheating of the living object completely (systemic) or partly (regionally or locally). “Overheating” is understood as “higher temperature than normal”. Hyperthermia is one of the most common therapies in “house” applications. It is applied according to unwritten traditions in every culture and every household. It is applied simply to prevent common cold but it is also good for its treatment, applied for various pains (joints, muscle-spasms, etc.), applied for better overall conditions and for simply relaxing, or sometimes for spiritual reasons. The various heat therapies are commonly used complementary with natural drugs (teas, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural and social events (ritual hot bath cultures), or to long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

The “prestige” of popular heat therapies is strongly supported by its corrective property: the person who has just received hyperthermia, feels the water-temperature most pleasant by hand when it is ~20 ^{o}C, while the 45 ^{o}C is pleasant for a hypothermic subject in the same experiment [1]. It seems that the heat therapy adjusts itself to the personal actualities; it is subjective, and adaptive.

These popular treatment applications of heating are types of “kitchen medicine”: the old recipes are “sure”, the patient takes it, and is cured when it is done according to the auricular traditional regulations. The meaning of “kitchen medicine” is, do it like in the kitchen, reading the process from the cookery-book: “heat it on the prescribed temperature for the prescribed time, and the success is guaranteed”. This type of thinking has its origin from the ancient cultures, when the Sun, the fire, the heat were somehow in the centre of the religious beliefs and philosophical focus.

This is “for sure” the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, “do it, get it”. However, the hyperthermia is not as simple as the traditions interpret it.

The fire and the radiation of the Sun had sacral significance in the ancient human cultures. In consequence the heat delivery was naturally on top of the curative possibilities. The ancient heat delivery however was ineffective and uncontrolled; deep heating was almost impossible. The method had its renaissance, when the modern electromagnetic heating techniques were applied controlling the heating process more precisely even in depth of the body. Important category of the hyperthermia was generated by electric fields [2], [3], which is even presently a hot topic in science [4], [5]. The electric conductive heating started in the late 19th century, called “galvanocautery” [6]. The method was further developed by D’Arsonval introducing the impedance (alternating current [AC], later higher frequencies, even sparkgenerated currents) calling it “Arsonvalization”, [7], and later a more modernized was “fulguration” [8]. The Arsonvalization method had fantastic popularity at the turn of the 19th -20th centuries, developing three different branches: the interstitial hyperthermia, including the galvanic heat-stimulation (electro-chemicalcancer- treatment), the ablation techniques and the capacitive coupling. The first capacitive coupled device on conductive basis was the “Universal Thermoflux”. It was launched on to the market by such a giant of the electric industry in that time as Siemens, which was later further developed, and the new device by the name “Radiotherm” was launched on the market in the early 1930s. The first start of the new capacitive-coupling technologies

was in 1976 by LeVeen [9] and has been widely applied since [10], [11], [12], [13]. Many hyperthermia devices use capacitive coupling since its application is easy and successful in clinical practices [14], [15], [16], [17]. The other line of the hyperthermia, based on radiative heat-absorption, form antenna array [18], [19]; showing many successful clinical studies too [20], [21].
From the late 1980s the heating up of the whole body or its certain region or a definite local volume started rapid development in the modern oncotherapeutic practices. The selective energy absorption has several favorable physiological and cellular effects promoting direct and indirect tumor-destructions without notable toxicity. Its main success lies in its complementary applications. Oncological hyperthermia is an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy and helps desensitizing the previously non-effective treatments. Hyperthermia in oncology has been debated in an increasing number of books and high-ranking clinical publications. From the standpoint of oncology, the official policy was to avoid applying hyperthermia in oncotherapies. The repulsive opinion focused on the increase of dissemination of malignant cells and so supporting the metastases, [22], [23], [24]. There were also reports about the induced hepatitis by hyperthermia [25].
This is the reason, that in contrary its long history, the state of oncological hyperthermia today is similar to that of therapies at their infancy. Like many early-stage therapies, it lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.
This relatively simple, physical-physiological method has a phoenix-like history with some bright successes and many deep disappointments. What do we have in hand? Is it a brilliant, miraculous, non-toxic treatment or a quackery of some charlatans?

Many of the researchers evaluating the capabilities of oncological hyperthermia share the opinion, expressed in the editorial comment of the European Journal of Cancer in 2001: the biological effects are impressive, but physically the heat delivery is problematic. The hectic results are repulsive for the medical community. The opinion, to blame the "physics" (means technical insufficiency) for inadequate treatments is general in the field of oncological hyperthermia, formulated the following statement: "The biology is with us, the physics are against us [26]. In the latest oncological hyperthermia consensus meeting the physics was less problematic. However, in accordance with the many complex physiological effects a modification was proposed: "The biology and the physics are with us, but the physiology is against us" [27].
The present situation apparently supports the above opinions. Probably oncological hyperthermia hasthe most questions in the titles of published literature. Numerous definite questions were formulated, such as:
• Is the community radiation oncologist ready for clinical hyperthermia? [28];
• What happened to hyperthermia and what is its current status in cancer treatment? [29];
• Where there's smoke, is there fire? [30],
• Should interstitial thermometry be used for deep hyperthermia? [31];
• If we can't define the quality, can we assure it? [32].
• Is there a future for hyperthermia in cancer treatment? [26],
• What is against the acceptance of hyperthermia? [33];
• Progress in hyperthermia? [34];
• Prostate cancer: hot, but hot enough? [35];
• Is heating the patient a promising approach? [36],
• Hyperthermia: has its time come? [37];

Oncologists face multiple serious decisions when meeting a new patient. The staging and many other factors help the decision what to do: apply evidence-based protocols "A" or "B", or try something personalized. When application of hyperthermia arises, the dilemma widens: "to heat or not to heat"? Considering hyperthermia as a treatment option new challenges occur: "How to heat? What to heat? How to control? How to evaluate? We would like to show where we are in the field, and show a definitely new paradigm for oncological thermal-treatment and give its perspectives for the future.

Technical challenges

There are various concepts to heat-up the tumor locally of regionally or by heating up the whole body. The most intensive local actions are the extremely large specific absorption rate (SAR) in a small volume, heating the target rapidly and intensively to the ablation (coagulation) temperatures (see Figure 1/a. [38]). In this case the short time of action does not allow the temperature distribution in the connective tissues.

These ablation techniques due to their large and localized request of SAR are mostly invasive, only the superficial lesions can be ablated non-invasively.
The local hyperthermia is mostly a non-invasive focused deep heating, having longer time to reach the heat-effects due to the time-limited SAR administration in deep regions (see Figure 1/b,c.). Heating a part of the body (regional or part-body heating [39]) targets a larger volume with the aim to eliminate the regional dissemination and metastases (see Figure 1/d.), while there is a whole body treatment to heat up the complete body systemically (see Figure 1/e.).

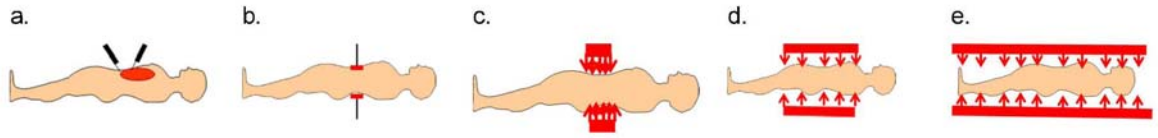


Figure 1. The main heating variations according to the targeted volume. The ablation (a) targets small volume with high SAR, while the local solutions (b. and c.) focus the electromagnetic energy from outside, and their SAR density is much lower, not making any coagulative processes, the part-body (d) and the wholebody (e.) treatments are non-focused techniques for temperature increase of a large targeted volume or the complete system

Thermodynamically the systemic and local/regional treatments differ in their energy-intake. The whole body treatment is based on the blood-heating (mostly heats up the subcutaneous capillary bed, or heats the mainstream of the blood directly with extracorporeal heater), while the local hyperthermia is definitely a tissue heating approach. This difference drastically divides the two methods from thermal point of view.
In whole body treatment the blood is a heating media, it delivers the heat to the tumor and heats it up; while in local treatment, the blood remains on body temperature during the local heating, so it is a cooling media (heat-sink) for the locally heated tumor, (see Figure 2.).

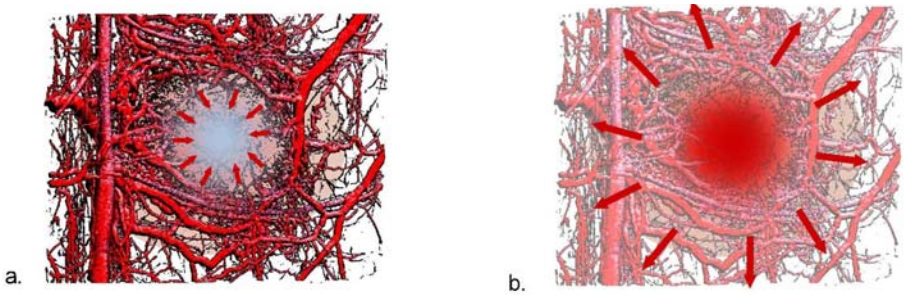


Figure 2. Opposite thermodynamic mechanisms of whole-body, systemic (a) and local (b) heating methods. The blood-heated tumor in whole body treatment reaches thermal equilibrium after a certain time, while the local treatment is always in non-equilibrium state, because the body temperature is lower than the heated tissue, creating intensive heat-flow from the target to the neighborhood

The whole-body heating could be solved by various ways, like steam, water or radiation heating. There are other possibilities as well (e.g. wax heating, hot-air heating, etc.) but the limited possible heat-flux and the poor technical realizations hinder these solutions. These are based on the blood-heating in the subcutaneous capillary bed, and the physiological reactions (vasodilatation and sweating) work well against the huge heat-flux into the body. The long heating time is also challenging (over an hour) to move the body away from the healthy homeostasis. The heat-flux is limited through the skin by the heat injuries (~0.5 W/cm 2 is the limit) so the contact heating with steam and water has definite problems. The radiation heating could be solved by special infrared wave (Infrared A) which penetrates deeper (~1-2 mm) into the subcutaneous layer, and could manage higher energy-flux without burn injuries. The method has many early descriptions [40], [41], [42], [43]; but the dominant systemic hyperthermia method is based on the infra-red radiation by multi-reflecting filtering [44], [45] or by water-filtering [46], [47], [48], [49]. In the followings we are going to concentrate on the local and regional heating techniques, which are mostly used in hyperthermia practices in oncology. Their various categories are roughly shown in Figure 3.

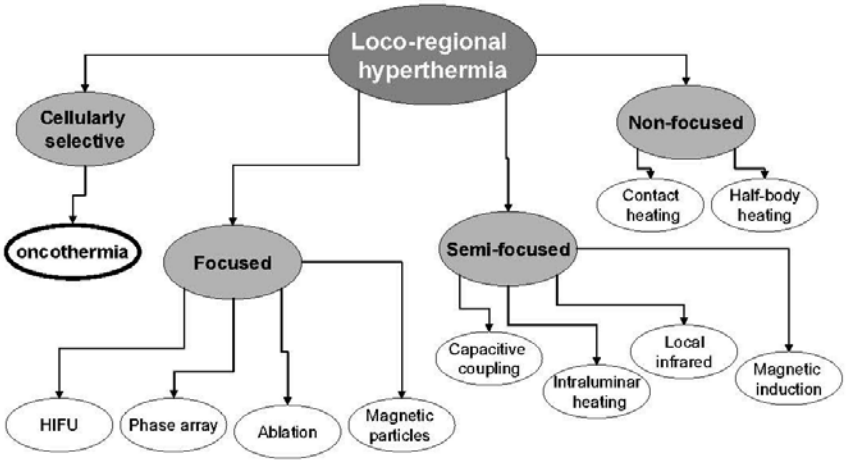


Figure 3. Various methods of the localregional hyperthermia with electromagnetic and ultrasound (HiFu) heating

The local/regional solutions are basically based on the electromagnetic effects, simple radiation (antenna effect) magnetic field application (coil effect) or electric field application (condenser effect), see Figure 4. These methods have high energy applications (kW range) to ensure the quick heating and the supply of the energy, which is gradually lost by the intensive cooling of the neighborhood of the target.

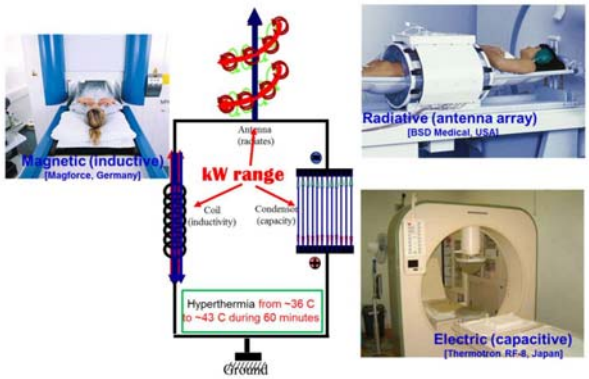


Figure 4. Electromagnetic fields are used in contemporary hyperthermia devices to heat up the body locally or regionally. All of these solutions are in range of kW energies, because the intensive physiological feedback tries to cool down the heated lesion

The race for the high power density in the focused area increases the risk of burns and the risk of misfocusing the fields resulting in hot-spots in the healthy volumes. The most part of the forwarded energy however is wasted due to the natural equalization of the temperature by the connected tissues to the target and by theintensive and steadily growing heat-exchanging mechanism of the blood-flow.

There are numerous electromagnetic hyperthermia methods applied. These are distinguished by the kind of the fields, frequencies, heated volume, conjunction with other methods, etc. In order to eliminate a part of the above challenges we try to go over the limits by technical tricks: cooling the surface to limit the surface load, focusing the energy on the lesion, controlling the hot-spots by imaging methods, etc. The main problems with the technical tricks are the loss of the basic control over the processes, requesting growing sophisticated methods to keep the pocess under control. This happen in the situation when we study the temperature which can be reached by any actual SAR energy. The blood-perfusion modifies the temperature, and even when the same energy is absorbed by the same volume, their temperature could be significantly different due to the different blood-flow through the target, see Figure 5.

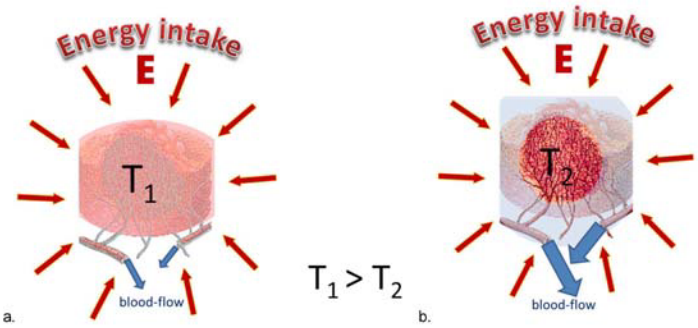


Figure 5. The same energy (**E**) is given to the same volume with different blood-flow. When the bloodflow is weak, (a), and strong (b) the reached temperature is high or low, respectively

Biological challenges

The original idea of the local hyperthermia was to force the tumor metabolism by heat. When the surrounding tissue is intact, it does not deliver more glucose for the forced metabolism Figure 6/a. The tumor very quickly deflates from nutrients, empties all its energies, suffers and burns away [50]; as well as the rapid increase of the lactate concentration [50] supports the cell destruction mechanism in the targeted volume.

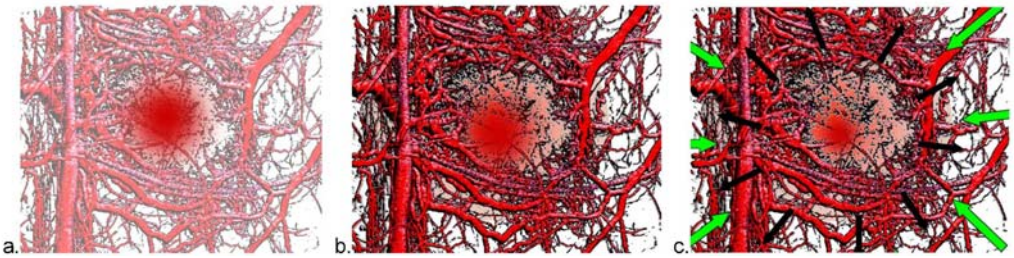


Figure 6. The focused local heating situation. (a) the local energy absorption impoverishes the ATP of the tumor, and it is destroyed. (b) The pumped energy has time to be distributed and heats up the surroundings, (c) the heated tissues deliver more glucose to supply the tumor and increase the risk of dissemination by increased blood-flow

When the heat delivery is intensive and short enough the local energy absorption heats up the target and ablation happens. If the energy is not enough for the coagulation, longer time is necessary for heating. In this case the locally absorbed energy heats up not only the chosen target but the surrounding tissue and even the whole body is heated up by the heat-exchanging mechanisms mainly by the blood-flow in the target Figure 6/b. The higher blood-flow delivers more glucose and nutrients to the tumor, causing opposite effect than the expected. In this way a competition starts: which one is quicker, the distortion or the supply, there is no control on the process Figure 6/c. Furthermore, the higher blood-flow is a real risk of the enhanced dissemination of the malignant cells (Figure 6/c.). This contradictory effect really blocks the controlling facilities of the processes, and so the result is incalculable and unpredictable. The real physical rule is that the energy can be focused precisely, but the temperature is not focusable, that is naturally distributed in the available volume trying to reach equilibrium (see Figure 7.).

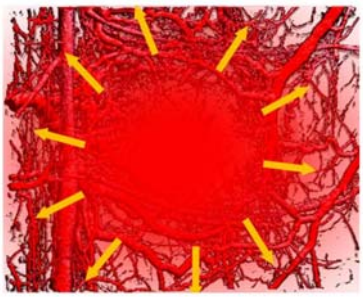


Figure 7. The locally heated volume heats up its neighborhood intensively. The energy is focused, but the temperature is not. The distribution of the temperature is forced by the physiological feedback trying to reestablish the homeostatic equilibrium

Complementary chemo or radiotherapy naturally helps controlling the process due to the higher chemoactivity [51]. The promoted, optimized chemo-intake helps to overcome on the fail of chemotherapies by the patient's intolerance (when it is not allowed to take big doses of drugs (for example at renal or liver insufficiency, insufficient blood-composition, etc.). In these cases the same results may be achieved by the combination of decreased chemo-dose and heat-therapy [52]. Hyperthermia supports the radioefficacy [53], [54] together with the applied heat. Hyperthermia has also been found to have pronounced advantages for surgical interventions. Through the hyperthermia induced inhibition of angiogenesis and heat entrapment, the outline of the tumor often becomes pronounced and the size of the tumor often shrinks making previously dangerous operations possible [55]. The feasibility of the preoperative application for locally advanced rectal cancer is well shown in a Phase II clinical trial [56]. Postoperative application of hyperthermia has also been thought to prevent relapses and metastatic processes [57]. Intraoperative radiofrequency ablation [58] and local hyperthermia [59] has also been used to improve surgical outcomes.

However, the complementary actions of other therapies in many cases could not compensate the bloodflow support of the tumor in a controlled way. Due to the physiological factors, the heat-treatment effects depend on the dynamism of the heat delivery, [60]. The quick heating acts differently on the local reactions and on the general thermoregulations from the slow one, because the physiological reaction time is relatively long. The highly non-equilibrium conditions in local-regional heating could not be stabilized, the stationer process is strongly influenced by the temperature regulation of the body. The measurements in humans evidently show the huge adaptability of the thermoregulation [61] (see Figure 8.).

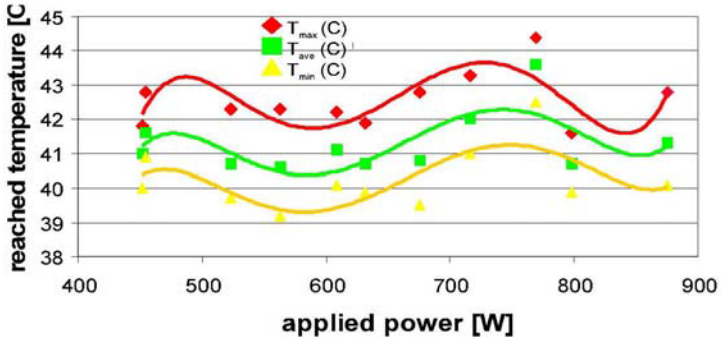


Figure 8. The homeostatic control keeps the temperature in a range, independently of the absorbed power

The temperature equalizing process naturally depends on the heat-exchange and heat conduction facilities, which are drastically enhanced by the growing temperature (see Figure 9. [62]).

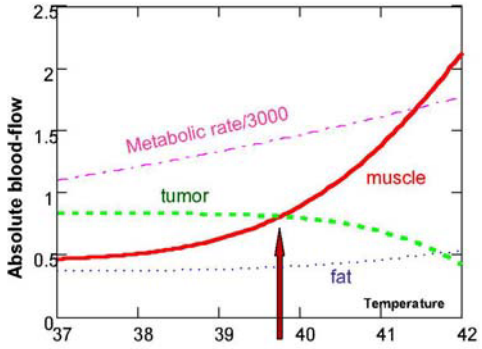


Figure 9. The blood-flow rapidly grows by the local temperature in the muscle tissue while the metabolic rate has linear increase only in the given temperature interval. The threshold (see text) is noted by an arrow

When the energy-transfer starts to heat up the whole body through the blood-heating of the target volume, new controlling processes (like sweating cutaneous vasodilatation, etc.) become active. The proper solution of hyperthermia would be when no increasing the complex feedback mechanisms against the heating action; having no unwanted gain of the blood-flow in the target. We have to act in the feedback loop mechanisms to reach the optimal situation, and not to excite the contra (negative feedback) actions, (see Figure 10/b.). The physiology acts against the local heating, which causes rapid heat-exchange of the target tissue with its connective tissues, and forces the body to make extra activity against local hyperthermia too. The reason for

the enhanced heat-conduction in the heated volume is simply physiological: the complex organism tries to reestablish the homeostatic equilibrium [63], it compensates the growing temperature with the higher cooling blood-flow (see Figure 10/a.). The absolute blood-flow values of the tumor and its connective neighborhood develops oppositely and turns over at threshold temperature value, allowing a drastic exponential increase of the blood-flow in the healthy tissue [64], [65].

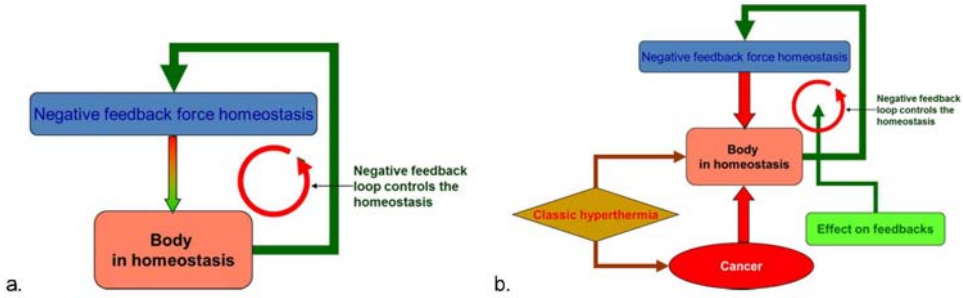


Figure 10. The feedback mechanisms of the complex living objects. (a) a definite

Hyperthermia in oncology has similar status that other medicaments, the difference between the medicine and poison is only the dose. There are certain energy-flow necessary for the deep heating, but of course the energy passing through the subcutaneous layers is limited by the toxicity, the burning. The blistering limit depends on the density of energy (W/cm^2) and the duration time of its application, Figure 11, [66].

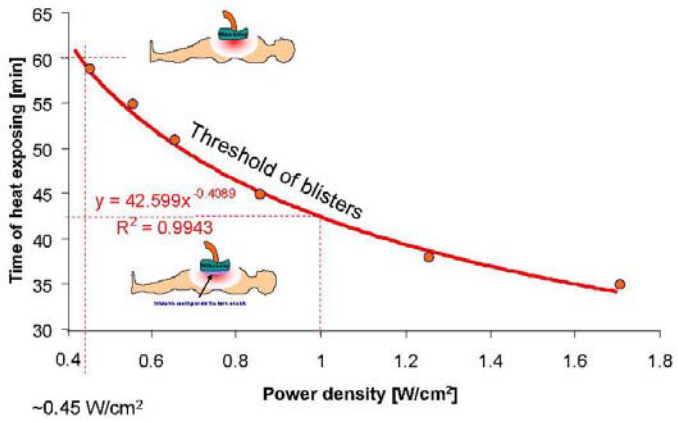


Figure 11. The blistering limit of the heating through the skin

To find the optimal path, it is necessary to fix the limits of the dosage. The lower limit is of course determined by the minimal effect by heating and the upper limit is determined mainly by the safety issues, like it is usual for overdoses. We have to consider that the modern hyperthermia is always complementary, so the other methods have to be considered at hyperthermia applications. The lower limit of the hyperthermia dose is probably the normothermia, where nothing else has action only the complementary treatment alone. With slight heating locally or systemically, it probably has no effect directly on the tumor, but it helps to increase the immune effects, enhances the complementary effects by the increased blood-flow and by the exponential temperature dependence of the chemical reactions (Arrhenius law). For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering shown above to the 0.5 W/cm2 , (60 min basis) the internal hot-spots could hurt the healthy tissue, and in the systemic application the physiology anyway limits it at 42 ºC. To avoid the overheating of the surface intensive surface cooling is applied in most of the electromagnetic hyperthermia techniques. In this case the physiology has negative feedback control again. In hot environment the subcutaneous layers have vasodilatation, high blood-flow helps the heat-exchange with the environment, it radiates out the excess body-heat, Figure 12/a. In cold environment the blood-flow is limited, the surface layer isolates the body Figure 12/b. Both cases change the heat- and electric-conductivity, as well as the dielectric properties of the skin layers. When the constrained forwarded power is applied, the voltage drops on the isolating (cooled) layer, it will be very high, a high voltage is necessary to pump through the requested constrain power. The relative high voltage lowers the current and less RF-current reaches the targeted deep-volumes.

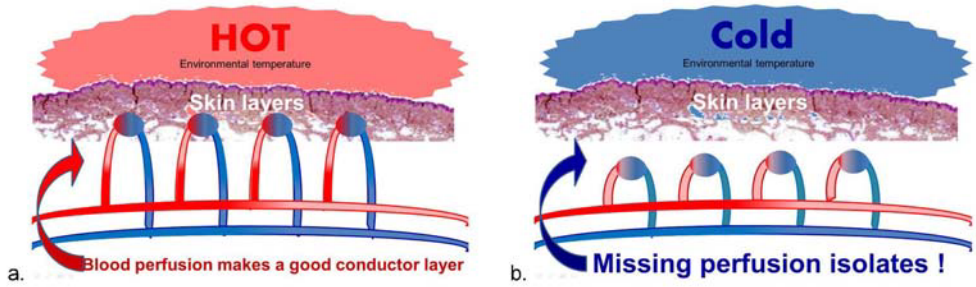


Figure 12. The environmental temperature significantly modifies the subcutane blood-perfusion. The hot environment (a) stimulates vasodilatation to cool down the body, while the cold environment works oppositely (b), definite vasocontaction helps isolate the body and avoids the loss of the body-temperature

On the other hand the high surface voltage will find the special conductive channels (blood-vessels, lymph passes, swealing paths, nerve-sensors, etc.) and like "sparking" passes through the isolating layer, causing electric bum despite the intensive cooling, see Figure 13.

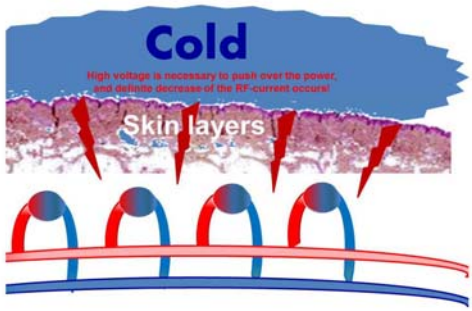


Figure 13. The constrained power produces high voltage on the skin layer. This finds narrow channels to go through, causing high risk of electric bum

The intensive cooling of the surface creates a further problem: the forwarded energy as parameter is not suitable when the cooling on the surface is intensive, because there is no idea about the energy lost by cooling. When we apply forwarded energy over one kW and the cooling has similar energy taken off, the control became very complex.
The other problem could be, when the energy heats mostly the bolus-liquid as the most energy-loaded surface layer and deeper seated body itself are not directly heated up. Again, the forwarded power does not give information about the real energy-load of the tumor.
Hyperthermia struggles with the technical problems above, and sometimes it hinders the biological factors.

The uncontrolled absorbed energy situation requests local control, the energy- intake which would be the natural dose measurement like in radiotherapy or like the chemical doses of medicine, cannot be applied here. Local, in-situ measurement is necessary to dose the treatment, and that only could be the temperature. The presently applied dose concept (CEM) is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in an extreme case reaches the 42 °C (even the 43 ºC is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start make vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40 °C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.
The ultimate challenge is to develop heat resistance, which could make the hyperthermia ineffective; the disease could become refractory for heating.

Medical challenges

Both the technical and biological challenges robustly appear in medical applications. However, some additional problems arise in medical considerations. The main point is connected to the inherent behavior of

the malignancy. The malignant tumor looks local but it is systemic; the main dangers of it are the dissemination of the malignant cells and the formation of distant, far away metastases. The survival prognosis is drastically worsens when the tumor is disseminated and metastasized. Considering this problem we have three-front fights:
1. Primary solid tumor, which proliferates and there is no natural block because the apoptosis is missing.
2. Dissemination transforms the local lesion to systemic disease. The dissemination occurrs mostly by missing adherent connections and missing cell-cell adhesions. When no dissemination happens the tumor is benign.
3. The formation of the distant metastases is the consequence of many various factors and one major is the missing immune reaction.

The dosing and control of the treatment is not only a technical and biological challenge. It is a hard problem of the medical application of hyperthermia. Without definite protocols it is a weak approach and has no possibility for comparison of the results and does not give reliable possibility for the patients. However the dose itself has numerous questions anywhere. The problem is mainly connected with the bio-variability which makes humans also individual. The dose has to be personalized, but then many points of the fixed protocol could not be fulfilled, as well as the collection of the cohorts for studies became complicated.
The dose in radiotherapy measured in Gy (J/kg), is a good quantitative parameter. However its efficacy depends on many physiological and technical parameters (like the oxygenation of the tissue, the focusing arrangement of the devices, the fractionating possibilities, etc. There are some surface burns representing the direct toxicity, which also can limit the application. Anyway the efficacy is measured by off-situ diagnosis (comparison of the before and after states), and the safety is fixed by the dose escalation studies, where the severe toxicity blocks the further increase.
The chemotherapy is definitely based on the toxicity limit. All the patients have the same dose depending on their surfaces. The dose is calculated by mg/m 2, irrespective of the size of the tumor, or any other personal specialties. We assume that the drug which is solved by blood is equally delivered to all of the body-volumes, and it is supposed that the tumor has been infiltrated by the drug in the same way as the other tissues do. The safety is again measured by dose-escalation studies. The concept is to apply the largest tolerable dose ("tolerable" means controllable side effects) and measure the efficacy off-situ later, in the same way (mainly by imaging) as the radiotherapy does.
In case of hyperthermia the highest tolerable temperature is defined, while the safety limit is also defined by the temperatures (hot-spots). Due to the long treatment time the patient roughly sensing the toxic dose (burning) so in hyperthermia the actual immediate correction of the dose could be done.
Another medical challenge of hyperthermia is its locality. The treatment is local, considering the tumor local too. But the malignancy is not local. Particularly it is not local when high-line treatment is applied after the failure of some earlier treatments, and the case is advanced, metastatic. In this point the local treatment alone is dubious even when the focusing is absolutely perfect and the action is concentrated completely on the desired target only.

Possible answers to the challenges

There is a new method emerging: oncothermia [69]. It is devoted to "pick up the gloves". It is a precise impedance (resistivity) matched system, Figure 14. This impedance fit is mainly based on RF-current and not on the voltage (potential) which is represented by a capacitor. Of course, this is also a capacitive coupling, but the electrodes of the capacitors are better conductors and promoting conductive behaviors than capacitors. While the capacitive coupling is based on dielectric loss of the material, the impedance matching is mainly Joule-heat, concentrating on the conductive part of the dielectric constant.

The capacitive coupling has two possible solutions: dominating the field (voltage) between the electrodes or dominating the current (ampere) from one electrode to the other. Oncothermia is this second type, using the current source instead of the voltage source. It is a special capacitive solution, using impedance matching for treatment. This heating is sensitive for the electrode direct touching, when they are not well connected to the body, the process stops, while the usual capacitive coupling acts when the certain high isolation (i.e. lifted electrode) is involved. The current-forcing solution forces the current through the target (starting from one electrode and finishing on the opposite, changing the situation by every period of the source). The two solutions have a lot in common, but the main difference is the current fixing. The same power has different effects, because the multiplication of the actual amperes and voltages define the constant power.

In conductive oncothermia the RF-current flows through the whole volume between the applied electrodes. In the oncothermia case the area of the cross-section that the RF-current flows through changes by depth, and it decreases the current density (current through a unit area). The energy deposition of the current in a unit volume, however, depends on the current density, which makes the energy absorption nonuniform in relation to depth.

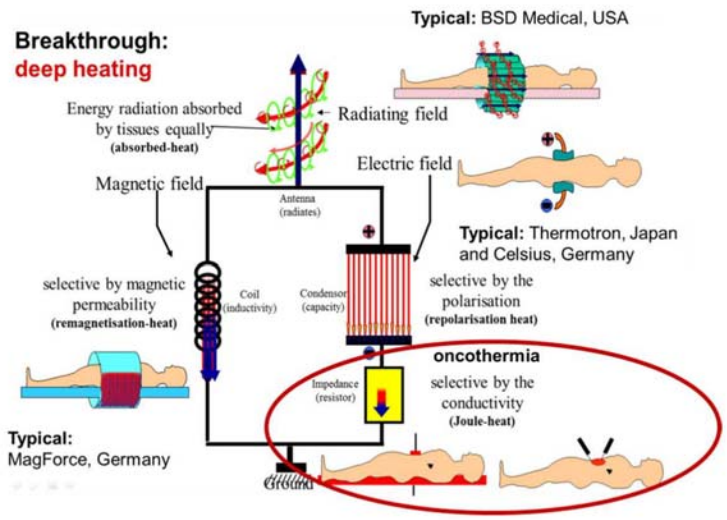


Figure 14. Impedance matching is the main factor of oncothermia

The better impedance coupling is supported by a technical trick, the asymmetric electrodes (see Figure 15.). The specific absorption rate (SAR) is much better in asymmetric solution starting on the surface, and the symmetric exceeds it in depth of 22 cm. Deeper than 22 cm the symmetric becomes better, which is for humans the full cross-thickness of a laying person.

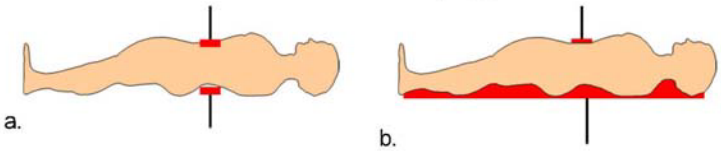


Figure 15. The symmetric (a) and asymmetric (b) electrode arrangement. The asymmetric arrangement has higher RF-current at same power

Oncothermia impedance coupling has special electrode construction to avoid any capacitive radiation, which could make non-controlled losses of unwanted shortage of penetration depth. It works by 13.56 MHz carrier frequency, applying definite, patented [67] time-fractal modulation with special template of its construction.

The complex modulated signal works effectively on the selection of malignant cells and promotes the heat-dispersion of the membrane bounded water-states. Together with the state of art fractal physiological considerations the concept is based on Warburg's principle of fermentative ATP production, and on Szent-Gyorgyi's principle of permittivity changes of malignant membranes [68]. There are numerous clinically proven advantages of oncothermia recognized [69]. The optimizing of dose, oncothermia uses the well-established gold-standard, the energy as used in the radiotherapies. The selection can heat up the malignant cells extremely high, without the same heating in the other parts of the tissue, Figure 16/a. However, by higher temperature the selection would be less emphasized, while the average is growing, see Figure 16/b,c.

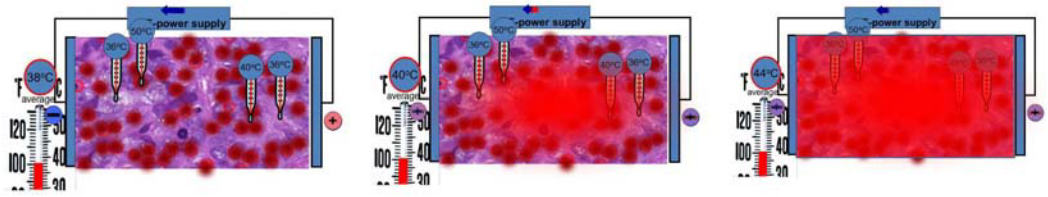


Figure 16. Heating with high selectivity in nano-heating process while the average temperature is kept low (a), incrasing the average temperature the selectivity lowers (b) and fixes the tissue in equilibrium, where no selectivity exists ever more (c)

The RF-current flows dominantly in the extracellular electrolyte, the cell-membrane is enough for the energy-absorption in it and in its surrounding thin electrolyte layers, see Figure 17.

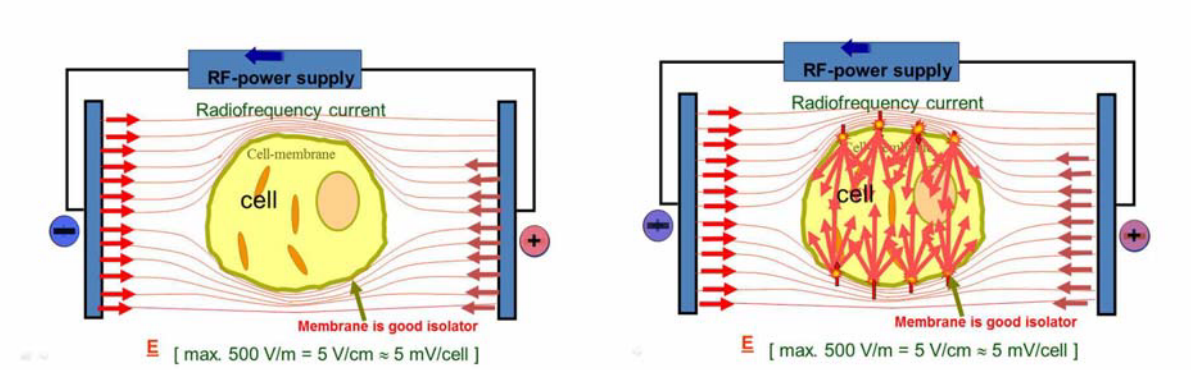


Figure 17. The RF-current penetrates into the cytoplasm only slightly, the majority of the energy is absorbed in the membrane and in its immediate vicinity (a). The temperature gradient excites the membrane (b)

The selection mechanisms [68] concentrate various effects on the membrane of the malignant cell, [70] Figure 18. The most important consequence of this excitation is the apoptosis which is formed in majority of the selective cell killing [71].

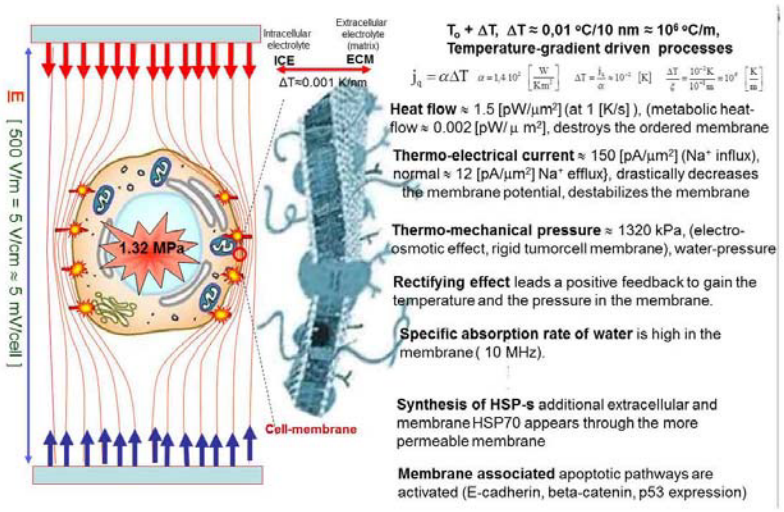


Figure 18. Various effects at the malignant cell are forced by the RF-field. The main effect is however to excite the pathways for apoptosis

An important observation shows the result of selection in oncothermia. While in conventional hyperthermia the relative cell-distortion is 17.9 % at 42 ºC, for oncothermia it is 57.1% in identical temperature, [72], Figure 19. Measurements were made by cooling the tumor intensively down to near body temperature (38 °C). In this measurement we take care of the same forwarded power as it was in the previous 42 °C process. It was intereting to observe the cell-distortion rate, which remained much higher than the conventional hyperthermia reaches in 42 °C.

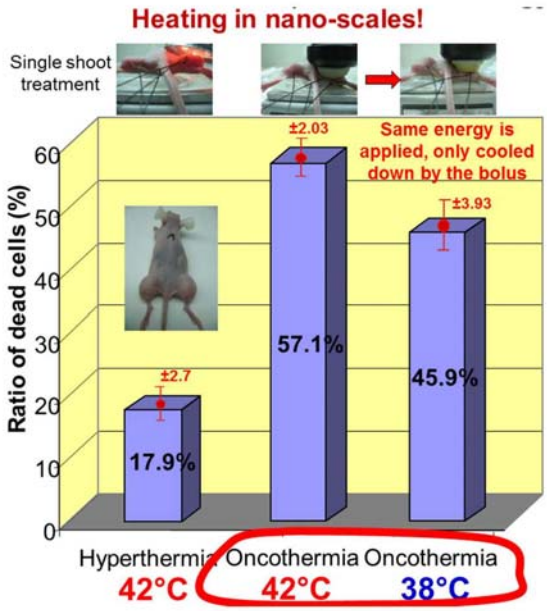


Figure 19. Oncothermia is more effective than conventional hyperthermia on the same temperature, and remains effective in case of lower average temperatures too

The careful, patented control of physiology of the skin at the treated volume [73] makes it possible to pump the highest available energy through the epidermis without toxicity. This lets us use the precisely matched and measured energy as control parameter; the cooling does not modify the energyintake.

The new technology allows using as much overall energy as necessary for the cellular heating, having no energy-loss by the heated non-cancerous volumes. The energy is selectively absorbed in nano-range of the membrane of malignant cells. The 1/10 th of the usually applied energy in similar devices is eligible to reach high quality results in preclinical and clinical use, mainly in survival time and quality of life. The main medical advantages of the method together with the effective selection and distortion of the malignant cells are the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. More details about this method were presented in this conference [68].

The dose is an important factor of efficacy safety and reproducibility in oncothermia. Conventional hyperthermia overemphasizes the temperature as a dose, which anyway is necessary for safety reasons, because the forwarded power and SAR do not correlate. The temperature is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic, average of the individual energies of the small units in the system. In chemo-therapy the cytotoxic remedies could cease very serious side effects, their safety has an emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or a complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.

When the medication definitely has no side effects (or the side effects are manageable) then the dose by their safety role has no upper limit. Anyway, when the dose is prescribed by fixed patient-independent protocol it is not realistically applied. When the prescribed energy is too high for the actual patient (high biovariability), the actually applied dose has to be lowered, trying to fit it for the actual patient.

Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) senses and notes the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much, actually it has to be modified on the personal requests. On the other hand, when the preset energy-dose is too small (the patients can actually tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety, and together with this, for the efficacy too.

Future tasks

There are numerous exciting tasks for the future of hyperthermia in oncology. Here is a list of them below without detailed description:

1. It is desired to extend to local treatment to whole-body effect, but affecting selectively only the malignant cells (irrespective of where they are in the body). This has numerous preliminary results by the bystander (abscopal) effect, which is definitely dose dependent and connected to the immune activation processes [74].
2. Oncothermia is completed by the preliminary results to solve the memory (vaccination) effect in situ prersonalized for the cancer patients. The memory effect was shown and used [75], [76], through T-cell activation.
3. More precise and specialized personalized effects have to be used by proper dose-adjustment and modulation-template [77].
4. More complementary applications have to be worked out. Conventional gold-standard therapies have to be widely applied in high line treatments too, working out the resensitizing processes for the previously refactory treatment. New therapies (dendritic-cell [78], stem-cell, [79], etc.) have to be involved in the combinative complementary processes.
5. There are multiple cases presented in this conference too [80], [81] showing the possibility to form the fatal cancer disease chronic, apply it for a long time (like dialysis) and make the patient's survival much elongated with good quality of life.

Conclusion

Nanoheating technology offers a renewing of the conventional hyperthermia. It is a synergy of the bioelectromagnetism with the fractal physiology. Oncothermia approach opens possibilities of stable controlled treatment without controversial challenges. It is a vivid way to solve the old-problems in hyperthermic oncology: it is a controlled, reproducible and reliable treatment.

References

[1] Ingram DL, Mount LE (1975) Man and animals in hot environments. Springer Verlag, Berlin, Heidelberg, New York

[2] Szent-Györgyi A (1960) Introduction to a submolecular biology. Academic Press, New York and London

[3] Schwan HP (1982) Nonthermal cellular effects of electromagnetic fields: AC-field induced ponderomotoric forces. Br. J. Cancer 45:220

[4] McCaig CD, Rajnicek AM, Song B, Zhao M (2005) Controlling cell behaviour electrically: current views and future potential. Physiol. Rev. 85:943-978

[5] Szasz N (2003) Electric field regulation of chondrocyte proliferation, biosynthesis and cellular signalling. PhD theses, MIT, Cambridge, USA

[6] Granmt D, (1904) The Galvano-Cautery in the Treatment of Intra-Laryngeal Growths. The Journal of Laryngology Rhinology and Ontology, 19 : 294-297

[7] Short History of Bioelectrics, http://www.pulsedpower.eu/bioelectrics/bio_02_main.html

[8] Kratzer GL, Onsanit T. (2007) Fulguration of selected cancers of the rectum: Report of 27 cases. Diseases of Colon and Rectum, 15:431-435

[9] LeVeen HH, Wapnick S, Piccone V et al (1976) Tumor eradication by radiofrequency therapy. JAMA 235(20):2198-2200

[10] Short JG, Turner PF (1980) Physical Hyperthermia and Cancer Therapy. Proc. IEEE 68:133-142

[11] Storm FK, Morton DL, Kaiser LR (1982) Clinical radiofrequency hyperthermia: a review. Natl Cancer Inst Monogr 61:343-50

[12] Abe M, Hiraoka M, Takahashi M et al (1986) Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (thermotron RF-8) in combination with radiation for cancer therapy. Cancer 58:1589-1595

[13] Ohno T, Sakagami T, Shiomi M et al (1993) Hyperthermai therapy for deep-regional cancer: thermochemotherapy, a combination of hyperthermia with chemotherapy. In: Matsuda T (ed) Cancer treatment by hyperthermia, radiation and drugs, Taylor&Francis, London-Washington DC, pp 303-316

[14] Jo S, Sugahara T, Yamamoto I (1994) Clinical response of hyperthermia using heating equipment Thermotron-RF8 in Japan. Biomed. Eng. – Appl. Basis & Commun. 6:340-362

[15] Takahashi M, Hiraoka M, Nishimura Y et al (1993) Clinical results of thermoradiotherapy for deep-seated tumors. In: Matsuda T (ed) Cancer Treatment by Hyperthermia, Radiation and Drugs. Taylor & Francis, pp 227-239

[16] Hiraoka M, Jo S, Akuta K et al (1987) Radiofrequency capacitive hyperthermia for deep-seated tumors – I. Studies on Thermometry. Cancer 60:121-127

[17] Lee CK, Song CW, Rhee JG et al (1995) Clinical experience using 8 MHz radiofrequency capacitive hyperthermia in combination with radiotherapy: results of a phase I/II study. Int J Radiat Oncol Biol Phys 32(3):733-45

[18] Turner PF (1984) Regional hyperthermia with an annular phase array. IEEE Trans Biomed Eng BME-31:106-111

[19] Wust, P., Fahling, H., Wlodarczyk, W.: Antenna arrays in the sigma-eye applicator: Interactions and transforming networks. Med. Phys 28, 1793-1805 (2001)

[20] Jones EL, Oleson JR, Prosnitz LR et al (2005) Randomized Trial of Hyperthermia and Radiation for Superficial Tumors. Journal of Clinical Oncology 23:3079-3085

[21] Issels RD, Lindner LH, Verweij J et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised highrisk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncology 2010; 11(6): 561-570
[22] Oliveira-Filho RS, Bevilacqua RG, Chammas R, (1997) Hyperthermia increases the metastatic potential of murine melanoma, Brazilian Journal of Medical and Biological Research, 30:941-945
[23] Shah SA, Jain RK, Finney PL (1983) Enhanced metastasis formation by combined hyperthermia and hyperglycemia in rats bearing Walker 256 carcinosarcoma. Cancer Lett. 19(3):317-23
[24] Nathanson SD, Nelson L, Anaya P, Havstad S, Hetzel FW (1991) Development of lymph node and pulmonary metastases after local irradiation and hyperthermia of footpad melanomas, Clinical and Experimental Metastasis 9:377-392
[25] Bragdon JH (1947) The Hepatitis of Hyperthermia – Report of a Fatal case. N Engl J Med 237:765-769
[26] Nielsen OS, Horsman M, Overgaard J (2001) A future of hyperthermia in cancer treatment? (Editorial Comment), European Journal of Cancer, 37:1587-1589
[27] Osinsky S, Ganul V, Protsyk V et al (2004) Local and regional hyperthermia in combined treatment of malignant tumors: 20 years experience in Ukraine, The Kadota Fund International Forum 2004, Awaji Japan, June 15-18
[28] Hornbach NB (1987) Is the community radiation oncologist ready for clinical hyperthermia? RadioGraphics 7:139-141
[29] Storm FK (1993) What happened to hyperthermia and what is its current status in cancer treatment? J Surg Oncol 53:141-143
[30] Brizel DM (1998) Where there's smoke, is there fire? Int J Hyperthermia 14:593-594
[31] Sneed PK, Dewhirst MW, Samulski T et al (1998) Should interstitial thermometry be used for deep hyperthermia? Int. J. Radiat. Oncol Biol. Phys. 40:1205-1212
[32] Oleson JR (1989) If we can't define the quality, can we assure it? Int. J. Radiat. Oncol Biol. Phys 16:879
[33] Szasz A (2006) What is against the acceptance of hyperthermia? Die Naturheilkunde Forum-Medizine 83:3-7
[34] Oleson JR (1991) Progress in hyperthermia? Int. J. Radiat. Oncol Biol. Phys 20:1147-1164
[35] Oleson JR (1993) Prostate cancer: hot, but hot enough? Int. J. Radiat. Oncol Biol. Phys. 26: 369-370
[36] van der Zee J (2002) Heating the patient: a promising approach? Annals of Oncology 13:1173-1184
[37] Smythe WR, Mansfield PF (2003) Hyperthermia: has its time come? Ann Surg Oncol 10:210-212
[38] Ellis LM, Curley SA, Tanabe KK (2004) Radiofrequency ablation of cancer. Springer Verlag, New York, Berlin
[39] Schlemmer M, Lindner LH, Abdel-Rahman S, Issels RD. Principles, technology and indication of hyperthermia and part body hyperthermia, Radiologe. 2004 Apr;44(4):301-9
[40] Devrient W (1950) Überwärmungsbäder. A.Marcus&E.Weber's Verlag Berlin
[41] Hoff F (1957) Fieber, Unspezifische Abwehrvorgänge, Unspezifische Therapie. Georg Thieme Stuttgart
[42] Lampert H (1948) Überwärmung als Heilmittel. Hippokrates Stuttgart
[43] Schmidt KL (1987) Hyperthermie und Fieber. Hippokrates Stuttgart
[44] Heckel M (1990) Ganzkörperhyperthermie und Fiebertherapie – Grundlagen und Praxis. Hippokrates Stuttgart
[45] Heckel M (1992) Fiebertherapie und Ganzkörper-HT, Bessere Verträglichkeit und Effizienz durch thermoregulatorisch ausgewogene, kombinierte Anwendung beider Verfahren. ThermoMed 14-19
[46] Vaupel P, Kruger W (1992) Warmetherapie mit wassergefilterter Infrarot-A-Strahlung, Grundlagen und Anwendungsmoglichkeiten. Hippocrates, Verlag Stuttgart
[47] Hildebrandt B, Drager J, Kerner T et al (2004) Whole-body hyperthermia in the scope of von Ardenne's systemic cancer multistep therapy (sCMT) combined with chemotherapy in patients with metastatic colorectal cancer: a phase I/II study. Int. J. Hyperthermia, 20:317-333
[48] Ardenne A. Von, Wehner H (2005) Extreme Whole-Body Hyperthermia with Water-Filtered Infrared-A Radiation. Eurekah Bioscience Collection, Oncology, Landes Bioscience
[49] Wust P, Riess H, Hildebrandt B (2000) Feasibility and analysis of thermal parameters for the whole-body hyperthermia system IRATHERM 2000. Int. J. Hyperthermia 4:325-339
[50] Vaupel PW, Kelleher DK. Metabolic status and reaction to heat of normal and tumor tissue. In: Seegenschmiedt MH, Fessenden P, Vernon CC, editors. Medical radiology—diagnostic imaging and radiation oncology, thermoradiotherapy and thermochemotherapy. Berlin and Heidelberg (Germany) and New York (NY): Springer; 1995. p. 157–76.
[51] Urano M, Douple E (eds) (1994) Hyperthermia and Oncology, Vol.4. Chemopotentiation by hyperthermia. VSP BV, Utrecht, The Netherlands
[52] Wiederman GJ, Siemens HJ, Mentzel M et al (1993) Effects of Temperature on the Threapeutic Efficacy and Pharmacokinetics of Ifosamide. Cancer Research 53(18):4268-4272
[53] Urano M, Douple E. (eds) (1992) Hyperthermia and Oncology: Volume .2. Biology of thermal potentiation of radiotherapy. VSP BV Utrecht The Netherlands, VSP BV Utrecht, The Netherlands
[54] Perez CA, Brady LW, Halperin EC et al (2004) Principles and Practice of Radiation Oncology. 4th edition, Lippincott Williams and Wilkins, Philadelphia
[55] Masunaga S, Hiraoka M, Akuta K et al (1990) Non-Randomized Trials of Thermoradiotherapy versus Radiotherapy for Preoperative Treatment of Invasive Urinary Bladder Cancer. J Jpn Soc Ther Radiol Oncol 2: 313-320
[56] Rau B, Wust P, Hohenberger P et al (1998) Preoperative Hyperthermia Combined with Radiochemotherapy in Locally Advanced Rectal Cancer – A Phase II Clinical Trial. Annals of Surgery 227(3):380-389
[57] Kodama K, Doi O, Higashyama M et al (1993) Long-term results of postoperative intrathoracic chemo-thermotherapy for lung cancer with pleural dissemination. Cancer 72(2):426-431
[58] Pearson AS, Izzo F, Fleming RYD et al (1999) Intraoperative radiofrequency ablation of cryoablation for hepatic malignances. Amer J Surg 178(6):592-598
[59] Kouloulias VE, Kouvaris JR, Nikita KS et al (2002) Intraoperative hyperthermia in conjunction with multi-schedule chemotherapy (pre- intra- and post operative), by-pass surgery, and post-operative radiotherapy for the management of unresectable pancreatic adenocarcinoma. Int.J Hyperthermia 18:233-252
[60] Hasegawa T, Gu Y-H, Takahashi T, Hasegawa T, Yamamoto I (2001) Enhancement of hyperthermic effects using rapid heating, In: Thermotherapy for Neoplasia, Inflammation, and Pain, Kosaka M, Sugahara T, Schmidt KL, Simon E, (Eds.), Springer Verlag, Tokyo-Berlin, pp. 439-444
[61] Katsuyuki K (1994) Thermotherapy in the treatment of locally advanced nonsmall cell lung cancer Int. J. Radiation Oncology Biol. Phys. 30(5):1171-1177

[62] Erdmann B, Lang J, Seebass M (1998) Optimization of temperature distributions for regional hyperthermia based on a nonlinear heat transfer model. Annals of NYAS, 858:36-46
[63] Hegyi G, Vincze G, Szasz A, (2012) On the dynamic equilibrium in homeostasis, Open Journal of Biophysics, 2:64-71
[64] Song CW (1984) Effect of Local hyperthermia on blood-flow and microenvironment: a review. Cancer Res 44(10 Suppl):4721s-4730s
[65] Song CW, Choi IB, Nah BS et al (1995) Microvasculature and Persfusion in Normal Tissues and Tumors. In: Seegenschmiedt MH, Fessenden P, Vernon CC (eds) Thermoradiometry and Thermochemotherapy, Vol. 1. pp. 139-156
[66] Stoll AM (1967) Heat transfer in Biotechnology, in: Advances in heat Transfer, (Eds.: Hartnett JP, Irvine TF.) 4:65-139, Academic Press Inc. New York, London
[67] Szasz A (2009) Radiofrequency hyperthermia device with target feedback signal modulation. International Patent Application No. PCT/EP2009/007342 based 08075703.2
[68] Szasz O. (2012) Essentials of Oncothermia, XXXI. Conference of the International Clinical Hyperthermia Society (ICHS), 12-14 October, 2012, Budapest, Hungary
[69] Szasz A, et al. (2010) Oncothermia: Principles and Practices. Springer, Heidelberg
[70] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electrobiology 22:103-115.
[71] Meggyeshazi N, Andocs G, Krenacs T. Programmed cell death induced by modulated electro-hyperthermia, XXXI. Conference of the International Clinical Hyperthermia Society (ICHS), 12-14 October, 2012, Budapest, Hungary
[72] Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Strahlenther Onkol. 2009 Feb;185(2):120-6.
[73] Szasz A (2009) Hyperthermia device for the selective treatment and monitoring of surface tissue. European Patent Application No. 07020933.3
[74] Goldenberg DM, Langner M., Direct and abscopal antitumor action of local hyperthermia, Z Naturforsch B. 1971 Apr;26(4):359-61
[75] Andocs G, Szasz A, Iluri N, Szasz O: Tumor Vaccination; patent, No. EP 12 181 821.5, Pending
[76] Andocs G, Szasz A, Iluri N, Szasz O: Tumor Vaccination; patent, No. US 61/744,008, Pending
[77] Szasz A, Iluri N, Szasz O: RF hyperthermia device for personalized treatment and diagnosis; patent, No. EP 12 181 833, Pending
[78] Matsumoto K, Yamamoto N, Hagiwara S, Saito M, Furue H, Shigetomi T, Narita Y, Mitsudo K, Tohnai I, Kobayashi T, Ueda M; Optimization of hyperthermia and dendritic cell immunotherapy for squamous cell carcinoma; Oncol Rep. 2011 Jun;25(6):1525-32
[79] R. Atkinson1, M. Zhang2, P. Diagaradjane4, S. Krishnan4, J. Rosen1, J. Rosen2, J. Chang1 and J. Chang; Hyperthermia Sensitizes Breast Cancer Stem Cells to Radiation Therapy; Cancer Research: 2009; 69, Issue 24, Supplement 3
[80] Lorencz P, Csejtei A. Experience with chronic Oncothermia treatments, XXXI. Conference of the International Clinical Hyperthermia Society (ICHS), 12-14 October, 2012, Budapest, Hungary
[81] TS Jeung, Cases that respond to Oncothermia monotherapy; XXXI. Conference of the International Clinical Hyperthermia Society (ICHS), 12-14 October, 2012, Budapest, Hungary

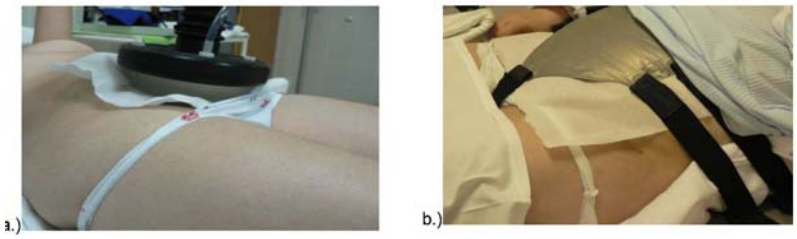


Figure 1. Arrangement of the treatment electrodes of oncothermia EHY2000 (a) and EHY3000 (b) type devices

The most important aspect of the treatment was the time schedule. The precise timing between chemo-, radio- and brachytherapy treatments was organized with high care, and oncothermia was applied immediately after chemo- or brachytherapy treatments, and at max 20 min before EBRT, and delivered during the whole course of the treatment schedule. The effectiveness was measured within confines of the oncological care. Imaging procedures as well as gynecological check-ups used to keep track of the development of the patients' status.

Note, this complementary treatment is currently not financed by the social insurance, therefore, patients had to pay privately for the oncothermia treatments. Unfortunately, this problem may affect the therapeutic plan in numerous cases, when the patient is unable to finance their own complementary treatment modality, even when the treatment is justified by professional aspects. In case of private cofinancing, the treatment plan of the commentary application is carefully designed to achieve the best available results.

Results

We first show a case report. The anamnesis of the 54 years-old female patient was G2,P2, with comorbidity hypertonia for 15 years. She had a stroke at the age of 54. She had vaginal bleeding symptom at the first diagnosis: Neopl.cerv.ut.std IIIB-IV; Fig. 2. Histology: carcinoma planocellulare. She rerceived the first external irradiation 2 Gy/day fractions, with 50 Gy complete dose. Additionally, afterloading brachytherapy was applied: 8 Gy, 5 Gy and 4.5 Gy, subsequently for three times.

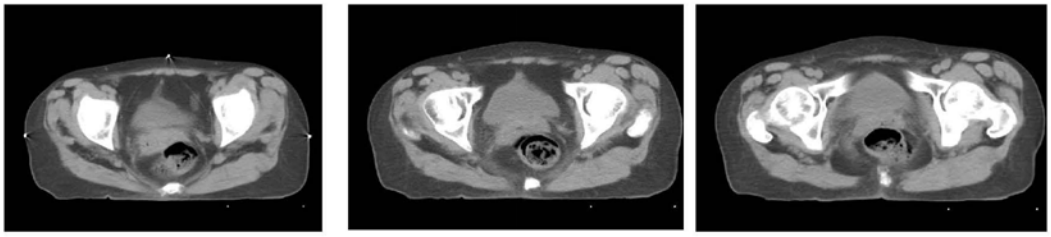


Figure 2. The diagnosis and the planning of the radiation and oncothermia complementary

Chemotherapy Cisplatin 40 mg/m2/week complementary to external radiation was performed, and oncothermia was given to her in 10 sessions. The result was a complete remission. With permanent checkup no evidence of disease (NED) can be found. The last control (four years after the finishing of the oncothermia) was NED again, Figure 3.

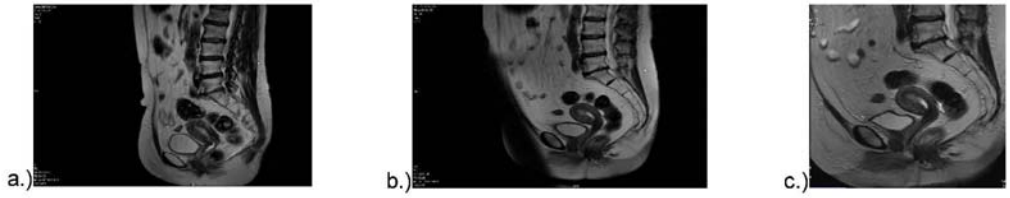


Figure 3. Control MRI of the patient: 1 months after oncothermia (a), one year after oncothermia (b), four years after oncothermia (c)

Patients had various number of treatments, Figure 4. in average 4.7 sessions were applied.

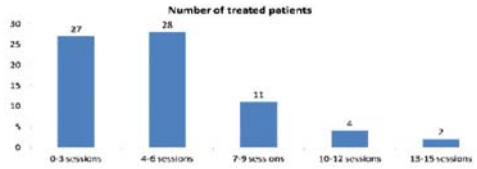


Figure 4. Distribution of the number of treatments for the patients (n=72)

The clinical response was measured in cases of trimodal applications (radiotherapy, chemotherapy and oncothermia, n=34). Results are promising: 73.5% (25/34) complete and partial remissions, 14.7% (5/34) stable disease and 11.8% (4/34) progressive disease, Figure 5.

Figure 5. Efficacy of radio-chemo-thermotherapy half year after finishing of the treatment

Our experience has shown that the addition of oncothermia had increased the effectiveness of conventional modalities, measured in the quality of life and survival elongation.

Conclusions

With a therapeutic plan prepared with due care and implemented precisely−especially the time between treatments and appropriate setting of treatment parameters−oncothermia can effectively complement the conventional oncotherapies. We will present our results in a case study, in which a patient's treatment was started only with palliative intent but at the end complete remission was available.

References

[1] Human Papillomavirus and Related Cancers; WHO Report, WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Summary Report Update. September 15, 2010.; HUNGARY, Human Papillomavirus; and Related Cancers in Hungary. Summary Report, 2010. [January, 2013].Available at www.who.int/hpvcentre

[2] Gibbs FA (1995) Thermoradiotherapy for Genituorinary and Gynecological Tumors. In: Seegenschmiedt MH, Fessenden P, Vernon CC (eds) Thermoradiotherapy and Thermochemotherapy, Vol 2. Clinical Applications, Springer Verlag,Telos

[3] Sekiba K, Hasegawa T, Kobashi Y (1993) Hyperthermic treatment for gynaecological malignancies. In: Matsuda T (ed) Cancer Treatment by Hyperthermia, Radiation and Drugs, Taylor & Francis, pp 261-270

[4] Harima Y, Nagata K, Harima K et al (2001) A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int J Hyperthermia 17(2):97-105

[5] van der Zee J, Gonzalez Gonzalez D, van Rhoon GC et al (2000) Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 355(9210):1119-1125

[6] Vasanthan, A., Mitsumori, M., Part, J.H. et. al.: Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multiinstitutional prospective randomized trial of the international atomic energy agency. Int. J. Rad. Oncol. Biol. Phys. 61, 145-153 (2005)

[7] Fatehi D, van der Zee J, van der Wal E et al (2006) Temperature data analysis for 22 patients with advanced cervical carcinoma treated in Rotterdam using radiotherapy, hyperthermia and chemotherapy: a reference point is needed. Int J Hyperthermia 22:353-363

[8] Rietbroek RC, Schilthuis MS, Bakker PJM et al (1997) Phase II Trial of Weekly Locoregional Hyperthermia and Cisplatin in Patients with a Previously Irradiated Recurrent Carcinoma of the Uterine Cervix. Cancer 79(5):935-943

[9] Jones EL, Samulski TV, Dewhirst, MV et al (2003) A pilot phase II trial of concurrent radiotherapy, chemotherapy, and hyperthermia for locally advanced cervical carcinoma. Cancer 98(2):277-282

[10] Tsuda H, Tanaka M, Manabe T et al (2003) Phase I study of combined radiation, hyperthermia and intra-arterial carboplatin for local recurrence of cervical cancer. Annals of Oncology 14:298-303

[11] Westermann AE, Jones EL, Schem BC et al (2005) First results of triple-modality treatment combining radiotherapy, chemotherapy, and hyperthermia for the treatment of patients with stage IIB, III, and IVA cervical carcinoma. Cancer 104:763-770

[12] van der Zee J, Gonzalez DG (2002) The Dutch Deep Hyperthermia Trial: results in cervical cancer. Int J Hyperthermia 18:1-12

[13] Prosnitz L, Jones E et al (2002) Counterpoint: Test the value of hyperthermia in patients with carcinoma of the cervix being treated with concurrent chemotherapy and radiation. Int J Hyperthermia 18:13-18

[14] van der Zee J, Koper PCM, Lutgens LCHW et al (2002) Point-counterpoint: What is the optimal trial design to test hyperthermia for carcinoma of the cervix? Point: Addition of hyperthermia or cisplatin to radiotherapy for patients with cervical cancer, two promising combinations – no definite conclusions. Int J Hyperthermia 18(1):19-24

Oncothermia Journal 7:293-294 (2013)

Experience in the treatment of liver metastases with special reference to the consequences of interruption of long-run treatments

Lorencz Peter[1], Csejtei András[1]

(1) Department of Oncoradiology, Markusovszky Hospital, Vas Country, 9700 - Szombathely, Markusovszky u. 3., Hungary

Corresponding author: Dr. András Csejtei, csejtei.andras@markusovszky.hu

Experience int he treatment of liver metastases with special reference to the consequences of interruption of long-run treatments

Abstract

Approximately 800 metastatic liver cases were treated with oncothermia in our department. Many of them had long-time, cumulatively, huge number of treatments handled the disease a chronic for years. We investigated the long-time effects of the treatments, together with them interruption of the treatment serial for a few weeks. We are reporting a typical case: mammary carcinoma with liver metastases. The metastatic lesion was treated for four years, but the termination of the treatment for two months was fatal at the end.

Introduction

Our department had the opportunity to integrate oncothermia treatments into the treatment flow of oncological patients since 2001. We have treated nearly 1000 patients of whom 80 percent had malignant liver lesions, primary liver tumor or various liver metastases. Regrettably, not only the medical and the technical aspects but the patient's financial background have had a role when professionals are selecting the available modalities. We selected a subgroup of patients into a study (will be published elsewhere) who had had at least 60 treatments, investigating the effect of the long term treatment and its interrupts - at least 2weeks- on the overall local outcome (clinical response). In this subgroup of patients with liver lesions oncothermia was integrated into a combined treatment regime with chemotherapy. Only bimodal therapy was used, no radiotherapy was applied. The complementary oncothermia was administered immediately after the chemotherapy. The patient's status was evaluated with standard laboratory check-ups and imaging modalities. The frequency of the tests was determined according to the Hungarian Social Security guidelines taking into account the overall condition and complaints of the patient. The case study to be presented here is a patient who had two times complete remissions confirmed with imaging modalities -CT, PET, US- and had oncothermia treatments temporarily terminated. Relapsing of the tumor-growth was observed at both times, despite the continuous standard oncological care. In the inspected group of patients the malignant disease was handled like usually for chronic ones. The cases where the regular oncothermia treatments were interrupted – for more than two weeks – the diagnostic check-up showed progression of the lesions, despite the ongoing conventional chemotherapy. We are giving a case report in details showing the chronic treatment process for liver metastasis from mammary carcinoma.

Report

Mammary carcinoma of the female patient was discovered by a routine mammography when she was 34 y old. Breast-conserving surgery was successfully performed (R0) and post-surgical radiotherapy (50 Gy [fractionated on 2 Gy] plus 10 Gy electron boost) as well. During the diagnostics liver metastasis was discovered. Chemotherapy was started: Taxotere + Epirubicine. (see Figure 1.) Oncothermia was started with the device EHY3000 (Oncotherm GmbH, Germany), and 49 sessions were given by 60 W, 60 min, twice a week.

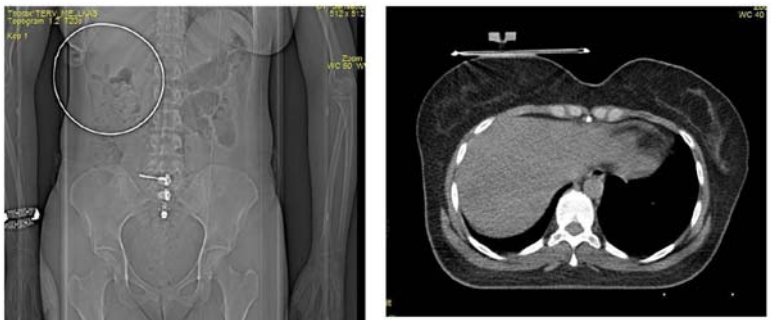


Figure 1.

During the oncothermia treatment regression was observed continuously and two month after finishing the oncothermia a PET/CT detected no evidence of disease (NED). The next checkup also found complete remission NED state, but a year later relapse was detected in the liver (see Figure 2.).

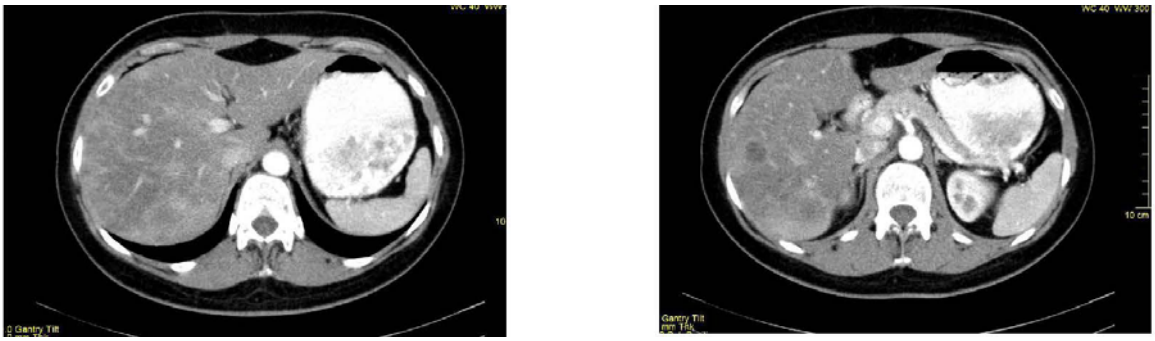


Figure 2.

Chemotherapy Taxotere +Xeloda followed by Taxotere + Paraplatin were administered, and complementary oncothermia 24 sessions once a week. A robust regression was observed in the follow-up period for one year (see Figure 3.).

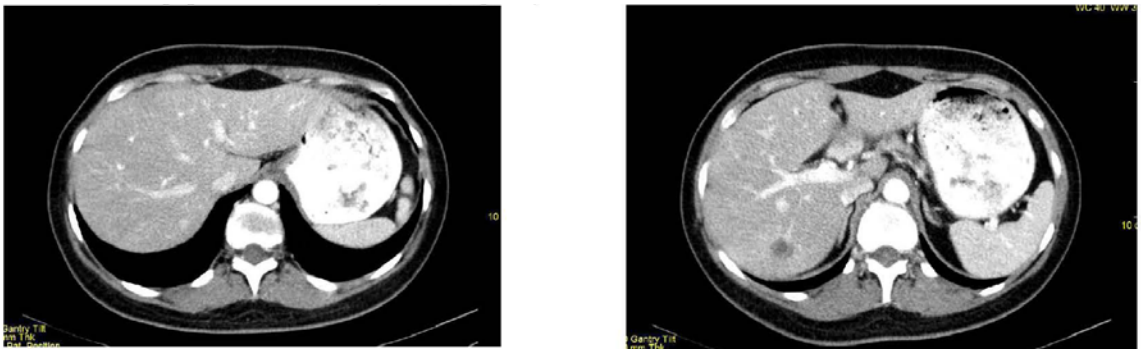


Figure 3.

When oncothermia was terminated, soon relapse was detected in the liver again with multiple lesions. The oncothermia was applied (60 W, 60 min, twice a week, 23 sessions), and the disease was stabilized. Oncothermia was terminated again, and only chemotherapy was applied (Taxol+ Gemzar). Rapid progression of the disease was observed (Fig. 4.), which led to exitus.

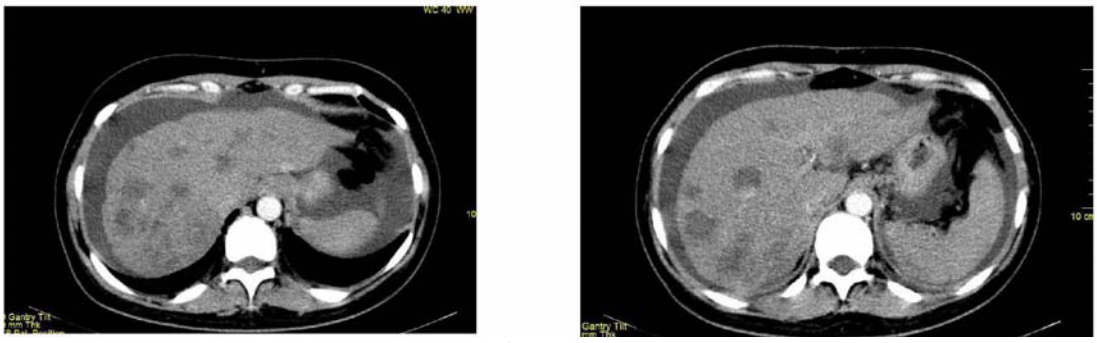


Figure 4.

Conclusion

Oncothermia can be applied for a long time, it handles the malignant liver tumor as chronic disease, but it should be continued during the whole chemotherapy course, or at least until the second negative control (2nd NED). Question arises: when should we to stop the oncothermia treatments and what diagnostic modality is suitable to confirm that there is no need for further treatments? The work is in progress.

Oncothermia Journal 7:296-300 (2013)

Oncothermia basic research at in vivo level. The first results In Japan

Andocs G[1], Okamoto Y[1], Kawamoto[1], Osaki T[1], Tsuka T[1], Imagawa T[1], Minami S[1], Balogh L[2], Meggyeshazi N[3], Szasz O[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

(2) "Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary

(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

(4) Biotechnics Department, Faculty of Engineering, St. István University, Budapest, Hungary

Corresponding author: gandocs@gmail.com

This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

Oncothermia basic research at in vivo level. The first results in Japan

Background

Oncothermia method (OTM) is a long time (since 1989) applied method in oncology [1] with great clinical success.[2] Oncothermia research group conducts investigations to reveal the basic mechanism of action of this tumor treatment method in basic research level performing a huge number of in vivo studies. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier and presented elsewhere [3], [4], as well as the recent in vivo results [5], [6]. In this paper we summarize the first results we have achieved in Tottori University, Japan.

Materials and methods

Study I.

In the first study we examine the effect of oncothermia treatment in a mouse tumor model. **Animal model:** Colon26 (murine colorectal cancer) cell line derived allograft mouse tumor modelwas used for this study with double tumors. The use of the mice and the procedures used in this study were approved by the Animal Research Committee of Tottori University.

Figure 1. Experimental mouse tumor model. Every animal had two tumors in both the femoral regions, the right side was teated, the left side was indivicual control

Experimental setup and treatment: A single shot 30min oncothermia treatment was done reaching maximum 42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement device (Lumasense m3300)

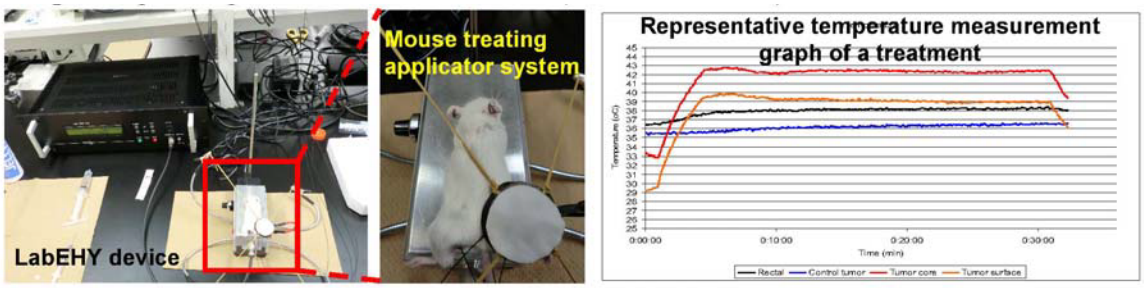


Figure 2. The experimental setup with the LabEHY system and a representative temperature measurement graph of the temperature curve of the tumors

Study design: A time course study was performed. After a single shot oncothermia treatment animals were sacrificed at 6H, 24H, 72H, and 120H later and tumors were removed. In all time-group there were 3 treated animals and 1 untreated control animal.

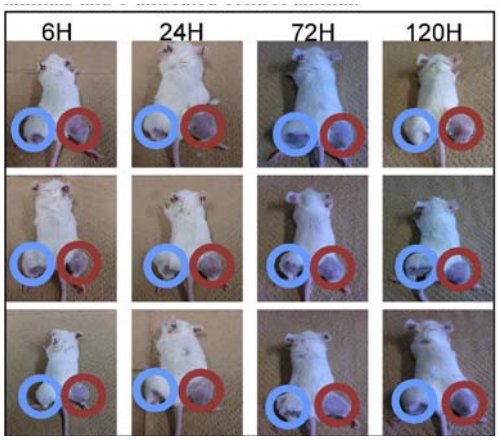


Figure 3. Oncothermia treated experimental animals in this study

Tumor sample processing: All the removed tumors were cut accurately at their centerline. After a standard histological process the samples were stained with HE and TUNEL reaction and Ki-67 immunohistochemical (IHCH) detection was performed (HE staining and IHCH detection were perfomed by Sapporo Byori Kensa Center, Japan). Samples were evaluated using complex histomorphological methods. Besides the qualitative analysis, a quantitative microscopical evaluation was also performed in the tumor samples stained with Ki-67. In ten randomly chosen high magnification (400x) microscopic view area of the living part of the tumor tissue samples the Ki-67 positive cell nuclei were counted, recorded and evaluated.

Study II.

In the second study we examined the effects of OTM to tumor oxigenization using a rat tumor model.

Animal model: 9L (rat glioma) cell line derived allograft rat tumor model was used. All animals had 2 tumors in both femoral regions. The use of the rats and the procedures used in this study were approved by the Animal Research Committee of Tottori University.

Oxygen level measurement: Tumor tissue oxigenisation level was measured using an O_2 sensitive electrode system (Eikon Kagaku Ltd. 150Dmodel).

Study design: In 11 rats, tumor tissue oxigenization level was measured using a pO_2 sensitive electrode system right before the treatment. The sensor probe of the system was inserted into the tumor tissue with the help and guidance of a teflone catheter, then the measured pO_2 value was recorded. Then the probe and the catheter were removed and a single shot, 30min oncothermia treatment was performed using a LabEHY system (Oncotherm Ltd.), reaching maximum 42°C intratumoral temperature. Right after the treatment the tumor oxigenization level was measured again.

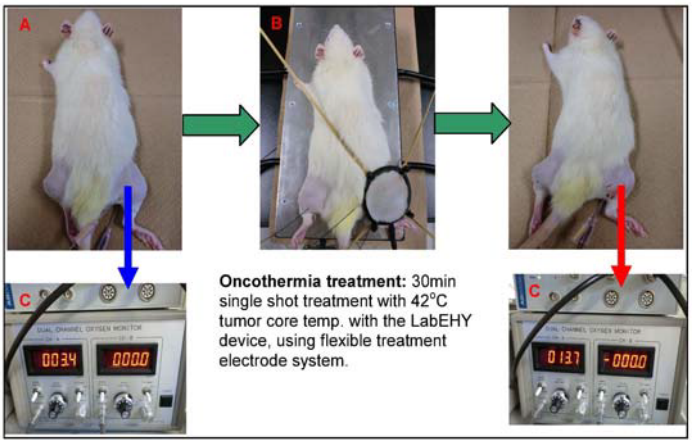


Figure 4. The study design. The 9L glioma cell line derived rat allograft tumor model (A), the oncothermia treatment procedure (B) and the tissue oxigenization measurement system (C)

Results

Study I.

1. A. Histomorphological changes in a qualitative and a quantitative way

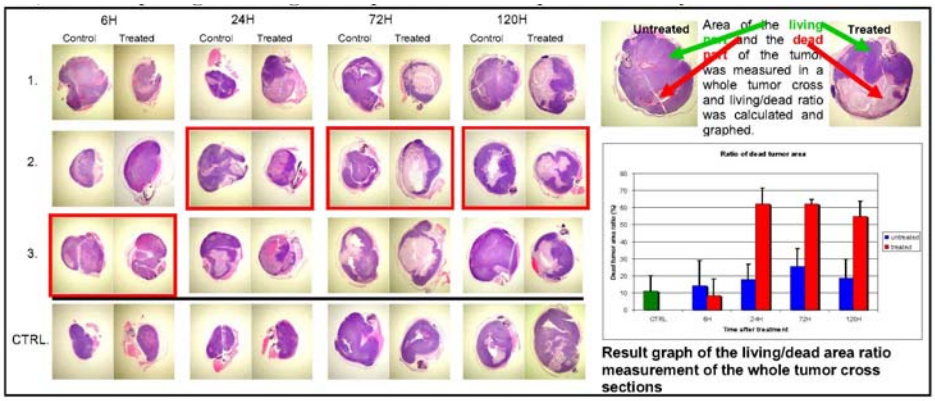


Figure 5. All the tumor samples involved in this study and the result graph of the quantitative analysis of the living/dead area ratio measurements. Drastic and selective tumor-destruction was detected adter a single shot oncothermia treatment. The tumor destruction was not immediate it had a time-delay. Samples marked with a red rectangle are evaluated in details

1. B. Histomorphological changes in details

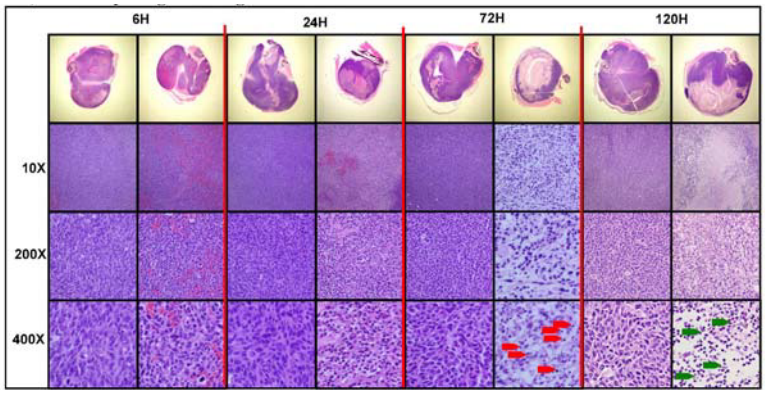


Figure 6. Detailed morphological analysis of the tumor samples marked with red rectangle in Fig. 5. 6H after the treatment the tumor cells look intact, but 24H after the treatment, the large part of the tumor is dead, the cells shrank with picnotic cell nuclei. In the 48H and 72H samples definite late morphological signs of apoptotic cell death was observed: extremely high number of apoptotic bodies (marked with red arrow). 120H after the treatment morphological signs of leukocyte (mostly neutrophiles, marked with green arrow) invasion is visible

2. TUNEL reaction

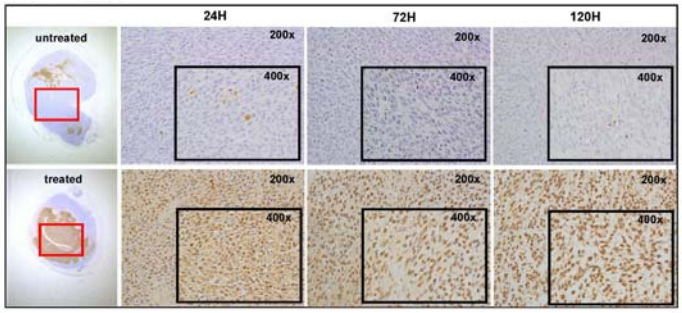


Figure 7. Result of the qualitative evaluation of TUNEL staining. TUNEL assay enzymatically labels the DNA fragments resulted by apoptotic cell death process. In the dead tumor area a huge number of TUNEL-positive cells were observed after a single shot OTM treatment

3. Ki-67 expression changes

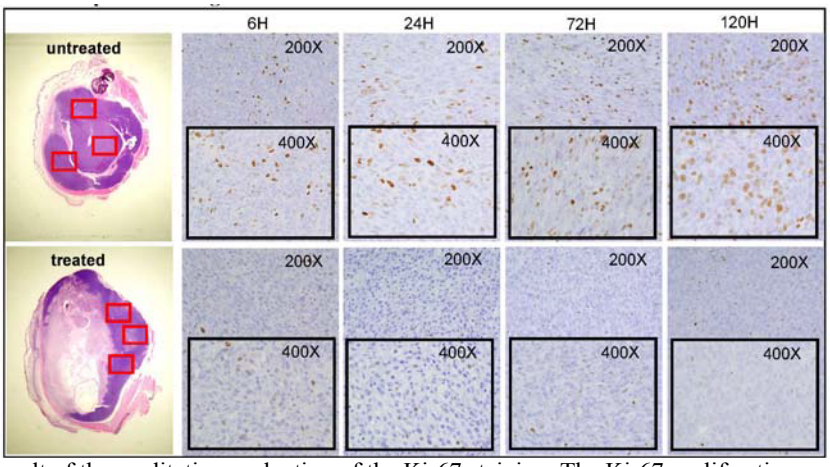


Figure 8. Result of the qualitative evaluation of the Ki-67 staining. The Ki-67 proliferation marker protein is expressed in the nuclear membrane only in the dividing cells. That is why sampling for Ki-67 positive cell analysis and counting were done from the living part of the tumors. The high magnification images from the living part of the tumor samples (marked with red rectangle in the whole cross sections)

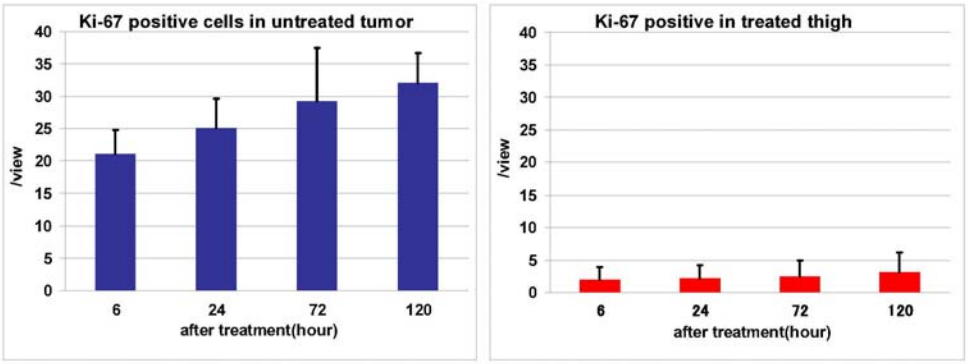


Figure 9. Result of the quantitative evaluation of the Ki-67 staining. Ki-67 positive cell nuclei were counted in 10 randomly choosen area of the living part of the tumor samples. In a very interesting way the number of Ki-67 positive cells were significantly decreased in the living part of the treated tumor compared to the control tumors

Study II.
Results of the tumor pO2 level measurement in a rat tumor model

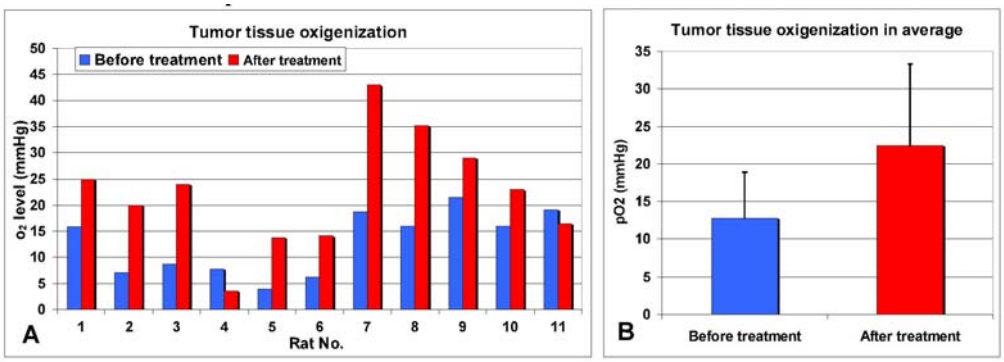


Figure 10. Result of the tumor tissue oxigenization level measurement in each animal (A) and in average (B). Tumor tissue pO_2 level was significantly higher right after the oncothermia treatment compared to the pO_2 level measured right before the treatment in case of 10 out of the total 11 animals. The pO_2 level was almost double after the treatment in average

Conclusions

1. In the mouse study, oncothermia treatment could significantly destroy the tumor tissue in a large volume of the tumor with only a single shot. Oncothermia treatment induce apoptotic cell death in the destroyed tumor tissue and effectively inhibit cell proliferation in the living part of the tumor.
2. In the rat study, oncothermia treatment could significantly increase the tumor tissue oxigenisation which created the basis of the strong synergism with radiotherapy and some chemotherapy.

References

[1] Szasz A. (2007) Hyperthermia, a modality in the wings J Cancer Res Ther. 3:56-66.
[2] Szasz A. Szasz N. Szasz O. (2010) Oncothermia. Principles and Practices, Springer Verlag, (http://www.springer.com/biomed/cancer/book/978-90-481-9497-1?changeHeader) Heidelberg, Dordrecht
[3] Andocs G, Szasz O, Szasz A. (2009); Oncothermia treatment of cancer: from the laboratory to clinic, Electromagn Biol Med. 28(2):148-65.
[4] Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing., Strahlenther. Onkol. Feb;185(2):120-6.
[5] Meggyeshazi N.: Programmed cell death induced by modulated electro-hyperthermia, ICHS 2012
[6] Meggyeshazi N.: Early changes in protein expression releated to modulated electro-hyperthermia, ICHS 2012

Oncothermia Journal 7:302-304 (2013)

Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

Coletta D[1], Gargano L[1], Assogna M[1], Castigliani G[1], De Chicchis M[1], Gabrielli F[2], Mauro F[2], Pantaleoni G[2], Pigliucci GM[1]

(1) Department of Oncological Hyperthermia, University of Tor Vergata, Rome, Italy
(2) Interfaculty Department for Scientific Researh (D.I.R.S.) – L.U.DE.S. University, Lugano - Switzerland

Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

Introduction

Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancer) in women and it is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis.

Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment and geographical location of the patient. Survival rates in the western world are high, in developing countries, however they are much poorer.

The size, stage, rate of growth and other characteristics of breast cancer determine the kinds of treatment. Treatment may include surgery, hormonal therapy, chemotherapy (CHT), target therapy, radiotherapy (RT) and thermotherapy (hyperthermia).

Surgical removal of the tumour provides the largest benefit in many cases.

To increase the likelihood of cure, several chemotherapy regimens (Antracycline based or not) and target therapy are commonly given in addition to surgery. Chemotherapy may be standard, which means administered full dosage and scheduled bi-tri-weekly, or metronomic therapy, which refers to repetitive, low doses of drugs, designed to minimize toxicity (Dr. Harold J. Burstein of the Dana-Farber Cancer Institute).

Targeted therapy (TT) is a form of treatment that is designed to specifically inhibit molecules that provide advantageous growth signals to cancer cells.

Current targets: receptor tyrosine kinases, VEGFR inhibitors, EGFR inhibitors, endothelin receptors, KIT, BCR/ABL, PDGFR, growth factors, VEGF, estrogen, androgen, transcription factors.

Radiation is used after breast-conserving surgery and substantially improves local relapse rates and in many circumstances the overall survival too.

Some breast cancers are sensitive to hormones such as estrogen and/or progesterone, which makes it possible to treat them by blocking the effects of these hormones (Tamoxifene or Aromathase Inhibitors or Fulvestrant).

Hyperthermia is a type of cancer treatment in which the body tissue is exposed to high temperatures (40-42°C).

A research has shown that high temperatures can damage and kill cancers cells, usually with minimal injury to normal tissue. Hyperthermia increase blood flow to the warmed area, perhaps doubling the perfusion in tumours, while in the normal tissue the increase might be tenfold or even more. This enhances the delivery of medications.

Thermotherapy also increases oxygen delivery to the area, which may make radiation more likely to damage and kill cells, as well as preventing cells from repairing the damage induced during radiation session.

Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy. These studies focused on the treatment of many type of cancer, including breast cancer, and shown a significant reduction in tumour size when hyperthermia was combined with other treatments.

Materials and methods

In our long experience in Universitary Hyperthermia treatment of tumours associated with chemotherapy, we have observed that the response to the associated treatment determines the disease stabilization and significant clinical benefit for 24 months in 12 cases of metastatic breast cancer, whereas chemotherapy alone has turned out to be ineffective with disease progression causing bone marrow toxicity G3-4, fatigue G2-3, nausea and vomiting G1-G2, bone pain G3-4 and visceral pain G2-3. (see Table 1).

TOXICITY WITH CHT ALONE	TOXICITY WITH ASSOCIATED THERAPIES (CHT+HT)
Bone pain: G3-4	Bone pain: G1-2
Visceral pain: G2-3	Visceral pain: G1
Fatigue: G2-3	Fatigue: G1-2
Nausea and vomiting: G2	Nausea and vomiting: G1
Bone marrow tox: G3-4	Bone marrow tox: G1-2

Table 1. 2 of 12 patients underwent hormone therapy alone because of their allergy to chemotherapy drugs, other 10 patients underwent to CHT+/- Hormone Therapy according to the protocols seen in Table 2.

ID	Birth Date	Therapy
C. L.	25/08/1969	*Exemestane,*
C. C.	19/02/1947	*CMF, Docetaxel, Nolvadex, Enantone*
D.L.V.	01/05/1956	*Trastuzumab+CBDCA, Myocet+Gemcitabine*
C. P.	22/10/1956	*FEC, Trastuzumab, Vinorelbine, Capecitabine, Fulvestrant*
F. V.	15/03/1946	*Myocet+ Docetaxel, Myocet+Gemcitabine, Zoledronic Acid*
F.D.	20/08/1962	*Fulvestrant+Xeloda, CBDCA+TAX, NVB+GEM*
P.G.	11/12/1957	*Herceptin+NVB, Herceptin,Xeloda*
O.F.	14/09/1959	*Zometa+Tam*
M.D.	19/08/1956	*Xeloda+TXT+BEVA,CBDCA+GEM, TAXOL, NVB, Myocet*
L.G.	28/08/1921	*TXT+Letrozolo*
P.D.A.	24/03/1961	*Herceptin+CBDCA, Myocet+Gemcitabina*
M.C.	19/94/1954	*FEC,CBDCA+GEM, Herceptin+NVB, Lapatinib+Xeloda*

Table 2.

All patients underwent an average 30 cycles of capacitive hyperthermia, each consisting of eight 45-minute sessions every other day, using 300W per session. Heat was applied to a small or large area, site of the tumor or metastases, using radiofrequency (SYCHROTERM RF 13.56 MHz). External applicators two flexible antennas with a diameter of 26 cm) were positioned in area to be treated to raise its temperature.

Results

In these patients the improvement of perfomance status has allowed a return to regular life. This improvement of the quality of life showed a correspondent biochemical response, with a progressive reduction in tumor markers and showed also a diagnostic response with stabilization of disease: in some cases the reduction of size and/or number of metastases and in all cases with absence of metabolic activity disease (TB PET CT scan).

Conclusion

Our data confirms that the association CT-HT is positively viewed by most women treated for MBC perceiving it as helping them to feel healthier and experience a sense of freedom.

The most interesting finding was the observed beneficial effect of HT on pain and an improvement of Quality of Life (QoL).

The use of OT/CHT-HT combination may enhance efficacy vs CHT and OT alone. This surprising result may confer a small, but probably, clinically significant improvement survival and quality of life. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.

According to the studies on P.N.E.I.M (1, 6, 7), the results in the field of Clinical Pharmacology concerning drug abuse and medicines disuse, and the resulting recent studies in anthropology on cancer patients, all of our patients were treated at a preventive, therapeutic and post-treatment level with appropriate behavioural tests and drug treatments to avoid relapse. Clinical Pharmacology, in our opinion, considers every patient, according to the multidimensional approach (biopsychosocial), as a global being (8, 9, 10, 11).

References

[1] Multidisciplinary therapy for 984 cancer patients;-hyperthermic immunotherapy. Takeda t, Miyazawa K, Takeda T, Takeda H, Takeda Y. Osaka Cancer Immuno-Chemotherapy Center.

[2] Multidisciplinary therapy for 984 cancer patiens; hyperthermic immunotherapy. Zagar TM, Higgins KA, Miles EF, Vujaskovic Z, Dewhirst MW, Clough RW, Prosnitz LR, Jones EL. Radiother Oncol. 2010 Dec;97(3):535-40. Epub 2010 Nov 11.

[3] Reirradiation combined with hyperthermia in breast cancer recurrences: overview of experience in Erasmus MC. Van Der Zee J, De Bruijne M, Mens JW, Ameziane A, Broekmeyer-Reurink MP, Drizdal T, Linthorst M, Van Rhoon GC. Int J Hyperthermia. 2010;26(7):638-48. Review.

[4] Hyperthermia for locally advanced breast cancer Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL. Int J Hyperthermia. 2010;26(7):618-24. Review.

[5] Antiangiogenic metronomic chemotherapy and hyperthermia in the pallation of advanced cancer Franchi F, Grassi P, Ferro D, Pigliucci GM, De Chicchis M, Castigliani G, Pastore C, Seminara P. Eur J Cancer Care (Engl). 2007 May; 16(3):258-62.

[6] Immunomodulation, Brain Areas Involved. Danuta Wrona., Encyclopedia of Neuroscience, 2009 Part 9, Pages 1926-1929

[7] Neuroendocrine modulation of the immune system: Possible implications for inflammatory bowel disease. Fergus Shanahan and Peter Anton. Digestive diseases and sciences. Volume 33, Supplement 3 (1988), 41S-49S,

[8] The Holistic Claims of the Biopsychosocial Conception of WHO's International Classification of Functioning, Disability, and Health (ICF): A Conceptual Analysis on the Basis of a Pluralistic–Holistic Ontology and Multidimensional View of the Human being. Hans Magnus Solli and António Barbosa da Silva. J Med Philos first published online May 7, 2012 doi:10.1093/jmp/jhs014.

[9] Self-criticism, neediness, and distress among women undergoing treatment for breast cancer: A preliminary test of the moderating role of adjustment to illness. Campos, Rui C.; Besser, Avi; Ferreira, Raquel; Blatt, Sidney J. International Journal of Stress Management, Vol 19(2), May 2012, 151-174. doi:10.1037/a0027996

[10] The psychological impact of mammographic screening. A systematic review. J. Brett, C. Bankhead, B. Henderson, E. Watson, and J. Austoker Psycho-Oncology, vol. 14, no. 11, pp. 917–938, 2005.

[11] Anxiety, emotional suppression, and psychological distress before and after breast cancer diagnosis. Y. Iwamitsu, K. Shimoda, H. Abe, T. Tani, M. Okawa, and R. Buck Psychosomatics, vol. 46, no. 1, pp. 19–24, 2005.

Oncothermia Journal 7:306-308 (2013)

Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

Carrie A. Strauss[1], Jeffrey A. Kotzen[1], AnsBaeyens[1,2], Irma Maré[1]

(1) Radiation Sciences, University of the Witwatersrand Medical School, 7 York Road, Parktown, 2193, Johannesburg, South Africa

(2) Radiation Biophysics, iThemba LABS, Somerset West, South Africa

Published: http://www.hindawi.com/cpis/medicine/2013/293968/

Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

Abstract

Aim: Investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa. **Objectives:** Evaluate the effect that the addition of oncothermia has on local disease control, progression free survival, overall survival at2 years, treatment toxicity, quality of life, economic impact and HIV status of participants. Radiobiology investigations will evaluate thermo-radiosensitivity and the molecular markers for thermo-radiosensitivity. **Methodology:** Phase III randomised clinical trial involving 236 HIV negative and positive stage IIb-III locally advanced cervical cancer patients. Treatment includes cisplatin, external beam radiation and brachytherapy. The study group will receive oncothermia treatments. Participants will be monitored for two years after completion of treatment. **Hypothesis:** The addition of oncothermia to standard treatment protocols will result in improved clinical response without increasing treatment toxicity in HIV positive patients or raising healthcare costs.

Introduction

More than 80% of hospital patients in Africa receive treatment in public healthcare facilities where resources and funding are limited.[1] The economic impact of cancer extends from the financial costs of treatment, rehabilitation, end-of-life care and loss of life to the economic costs of days off work, loss of productivity and the social-economic pressures on the family and community of cancer patients.[2] Sub-Saharan Africa has the highest HIV prevalence in the world.[3] It is a growing concern that the HIV status of a person and theanti-retroviral medications increase the patients' sensitivity to toxicity from radiation therapy and chemotherapy.[4,5,6] There is therefore a strong need for the investigation and application of technologies which can increase cancer treatment efficacy without increasing the treatment costs in Africa. Research from the Netherlands indicates that hyperthermia technology may increase the treatment efficacy whilst lowering the healthcare costs of cervical cancer patients.[7] The investigation of the use of affordable hyperthermia technology is therefore warranted.

Background

Cervical cancer is classified as an AIDS defining illness by the World Health Organisation. Over 80% of the 555 000 new cervical cancer diagnoses globally per year will occur in developing countries where HIV is prevalent.[8] Cervical Cancer is the second most prevalent female
cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published.[9] Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.10 cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published. 9Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.[10]

Aim

To investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment protocols for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa.

Methodology

Study-design: Phase III randomised clinical trial. **Sample:** 236 HIV negative and HIV positive stage IIIb-III locally advanced cervical cancer patients will be recruited. This is based on the estimated required sample size for a two-sample comparison of survivors' function at two years. The statistical significance is defined as a two-sided alpha <0.05for a log–rank test, with a constant Hazard ratio of 0.5693, a statistical power of 90%, a 15% withdrawal rate and an estimated 140 events.We anticipate at least 50% of recruited participants will be in Stage III of the disease and around 30% of participants will be HIV positive. **Randomisation:** The participants will be divided into a control group (N=118) and a study group (N=118) and the sampling method used will be stratified random sampling (stratum: HIV status). Location: Charlotte Maxeke Johannesburg Academic Hospital, Gauteng, South Africa. **Treatment:** Participants from both groups will receive 3 doses of cisplatin (80mg/m2) administered three weeks apart, external beam radiation (50Gy administered over 25 factions of 2Gy) and 3 HDR intracavitary brachytherapy treatments of 8Gy each. The study group will receive two 60 minute modulated electro-hyperthermia (oncothermia) treatments per week during the external beam radiation therapy (total 10 treatments). **Duration:** The study is scheduled to start in early 2013 and the recruitment period is expected to take two years. Participants will be monitored for two years after completion of treatment protocols. The total study duration is expected to be four years. Preliminary results for the local disease control and radiobiology research are expected to be available within the first three years. **Radiobiology Research:** Radiobiology research will be conducted on tissue and tumour samples in order to study the effect that heating tumours has on the systemic and local response and toxicity resulting from treatment with ionising radiation.

Objectives

Primary Objectives: Evaluate the effect that the addition of oncothermia has on local disease control at 6 months (assessed by PET scans); progression free survival at 12, 18 and 24 months and overall survival at2 years (and the cause of death)in HIV positive and negative cervical cancer patients. Secondary **Objectives:**·To evaluate the adverse effects that can be directly attributed to oncothermia treatments. To evaluate the effects of oncothermia on tolerability andtoxicity of the prescribed treatments. To evaluate the economic impact of the addition of oncothermia to standard treatment protocols in public healthcare (based on quality adjusted life years). To evaluate the effect of the addition of oncothermia on the quality of life of patients (EuroQOL EQ-5D-5L questionnaire and the EORTC QLQCX23 cervical carcinoma specific questionnaire).·To evaluate the effect, if any, of oncothermia treatments on the HIV disease status of HIV positive participants by assessing the CD4 count; HIV viral load and the concurrent AIDS-defining conditions. To describe cervical cancer recurrence patterns in both groups by loco-regional and distant recurrences and by initial stage and suspicion for nodal metastasis pre-treatment. **Radiobiology:**·To evaluate thermo-radiosensitivity by measuring DNA damage (double strand breaks) in lymphocytes in response to ionising radiation combined with oncothermia. Haematological samples will be taken from patients in all four groups before and after the administration of radiation therapy. Double strand breaks will be measured using Micronucleus (MN) assays and the results will be analysed in order to determine whether the addition of oncothermia had an effect on the systemic toxicity of ionising radiation therapy in HIV positive and HIV negative cancer patients.· To investigate the molecular markers for thermo-radiosensitivity. This will be done by comparing gene expression profiles of cells extracted from biopsies of thermo-radiosensitive and thermo-radio-resistant tumours. Gene profiling of tumour samples will be used to identify potential molecular markers in the tumour cells which are associated with increased response or with resistance to radiochemotherapy combined with oncothermia.

Expected outcomes

It is expected that the addition of oncothermia to standard treatment protocols will result in improved local disease control and improved two year survival rates without increasing the treatment toxicity. We hypothesise that the addition of oncothermia will result in a reduction in healthcare costs associated with the treatment of cervical cancer.

Study rationale

This will be the first trial to date to investigate the effects of hyperthermia on HIV positive cancer patients and will be the first hyperthermia trial to be conducted in Africa. This will be the first phase III trial investigating oncothermia in cervical cancer patients and the first phase III trial investigating the trimodality treatment of cervical cancer patients. The study will investigate the economic impact of the addition of oncothermia to public healthcare protocols in Africa. The radiobiology research and genetic profiling is also unique in the field.

Acknowledgements

The hyperthermia device being used is the EHY2000 Plus which is being supplied by Oncotherm GmbH.

References

1 Keeton C. (2010) Bridging the Gap in South AfricaBulletin of the World Health OrganizationVol. 88, No 11, Pp: 797–876 Available online from: http://www.who.int/bulletin/volumes/88/11/10-021110/en/index html

2 American Cancer Society (2007) Global Cancer Facts & Figures 2007, pp: 8; 23, Available online from: http://www.cansa.org.za/cause_data/images/1056/Research_-_Global_Facts_&_Figures_2007.pdf (Accessed 1st April 2012

3 World Health Organisation (2011)GLOBAL HIV/AIDS RESPONSE: Epidemic update and health sector progress towards Universal AccessProgress report 2011 Available online from: http://www.who.int/hiv/data/tuapr2011_annex8_web xls (Accessed 5 January 2013)

4 Mallik S., Talapatra K., GOswami J. (2010) AIDS: a radiation oncologist's perspectiveJournal of Cancer Research and Therapeutics Vol. 6, No. 4, pp: 432-441 Available online from: http://www ncbi nlm nih.gov/pubmed/21358076 (Accessed July 2012)

5 Baeyens A., SLabbert J.P., Willem P., et al. (2010) Chromosomal radiosensitivity of HIV positive individualsInternational Journal of Radiation Biology Vol. 86, No. 7, pp: 584-592 Available online from: http://www ncbi nlm nih.gov/pubmed/20545573 (Accessed July 2012

6 Ousri N., Yarchoan R. and Kaushal A., (2010) Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary?Cancer Vol. 116, No. 2, pp: 273-283 Available online from: http://www ncbi nlm nih.gov/pubmed/20014399 (accessed July 2012)

7 Van der Zee J. and Gonzalez G.D. (2002) The Dutch Deep Hyperthermia Trial: results in cervical cancerInternational Journal of Hyperthermia Vol. 18, No. 1, pp: 1-12

8 UNAIDS (2009) South Africa, Available online from: http://www.unaids.org/en/regionscountries/countries/southafrica (Accessed July 2012)

9 National Cancer Registry of South Africa (2010)2001 National Cancer Registry Tables Published in Cancer in South Africa, 2000-2001; Available online from: http://www.cansa.org.za/cause_data/images/1056/NCRCharts_2001.pdf (Accessed 1st April 2012)

10 Kotzen J. (2012) Personal communication; Radiation oncology, Charlotte Maxeke Johannesburg Academic Hospital

Oncothermia Journal 7:310-316 (2013)

Oncothermia as personalized treatment option

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]
(1) Department of Biotechnics, Szent Istvan University, 2100-Godollo, Pater K. u. 1., Hungary
(2) Department of Veterinary Clinical Medicine, School of Veterinary Medicine, Tottori University, Tottori, 4-101 Minami, Koyama-cho., Tottori Pref., Japan
(3) 1sr Department of Pathology and Experimental Cancer Research, Semmelweis University, 1085-Budapest, Ulloi ut 26., Hungary
Corresponding author: biotech@gek.szie.hu

Published: http://www.hindawi.com/cpis/medicine/2013/941364/

Oncothermia as personalized treatment option

Abstract

Oncothermia is a nanoheating technology personalized for individual status depending on the state, stage, grade, and other personal factors. The guiding line of the treatment keeps the homeostatic control as much effective as possible. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. The applied step-up heating supports the physiological selection. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed. It has wide-range applicability for every solid tumor, irrespective of its primary or metastatic form. It could be applied complementary to all the known oncotherapy methods. It is applicable in higher lines of the therapy protocols, even in the refractory and relapsed cases as well.

Keywords: oncology, hyperthermia, oncothermia, personalization, Weibull-distribution, logistic-curve, response-time, surface-cooling

Introduction

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment using energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3], and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized [5]. The central task is to find the proper dose in the given application, and optimize the safety and curative limits of the applied dose. The lower limit is of course determined by the minimal effect by heating and the upper limit determined mainly by the safety issues, like it is usual for overdoses. The lower limit of oncothermia dose is indefinite, because in case of normothermia nothing else has action only the complementary treatment alone, which has no danger and has such curative effect as we expect from the gold-standards. For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering to the 0.5 W/cm^2, (60 min basis) the internal hot-spots could hurt the healthy tissue, and in systemic application the physiology anyway limits at 42°C. The ultimate challenge is the developing heat resistance, which could make the hyperthermia ineffective, the disease became refractory of heating. The presently applied dose concept (CEM) in conventional hyperthermia is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in extreme case reaches the 42°C (even the 43°C is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start makes vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40°C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.

Hyperthermia overheats the actual target. It does not limit the target size at large (like whole-body hyperthermia) or at small (like heating with nano-particles) volumes. These methods are all characterized by the temperature, but they are characteristically different by their thermal state. In whole-body heating the thermal equilibrium drives the process, the body-temperature characterizes the treatment technically. However the body temperature characterizes the process less and less by decreasing the volume of the heated target, the body temperature becomes stable and almost independent from the local heating of a smaller volume in the body. Contrary to the thermal equilibrium in whole body heating, the nonequilibrium dominates in local treatments, and consequently thermal gradients will appear in the system.

Heating in nanoscopic range creates huge fluctuations of the local temperatures while the hot nanoparticles try to equalize their high temperature with their neighborhood. This process is typical for the commercial microwave heating, where not the extra nanoparticles, but especially the water-molecules are heated in their nanoscopic sizes, and those give the temperature to the entire volume by time. To

construct a nano-heating process the targeting of the nanostructures is a clue. Their selection from the other materials makes their controlled heating and also targeting the heat on the desired volume possible.
Extra nanoparticles could selectively absorb the electromagnetic energy heating up these small particles extremely in their neighboring spheres. Our approach is definitely similar, but by not using extra particles for selective energy absorptions. Our nanoscopic targets are naturally in the body, in the membrane of the malignant cells. The selection is based on the metabolic differences (Warburg effect), the dielectric differences (Szent-Gyorgyi effect) and beta-dispersion (Schwan effect) as well as uses the structural (pathological) differences (fractal effect) of the malignant lesions.
The main medical advantages of the method are its personalized targeting together with the effective selection and distortion of the malignant cells. The new direction of application focuses on the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. The method is successfully developed in the direction of the immune-support, and a new patent covers an exciting area: cancer-vaccination with oncothermia.

Method

The physiological processes are determined by a dynamic equilibrium process-character, which is dominantly determined by special transports and logistics in the complex bio-systems. The distribution which is typical for general logistics, failure analyses and even for survivals is the Weibull distribution [6], which cumulatively looks

$$f(x) = e^{-(x/t_0)^a} \qquad (1)$$

where to is the unit time, when the value of the function is 1/e<0.63; the a-exponent in the distribution defines the shape (see Figure. 1.).

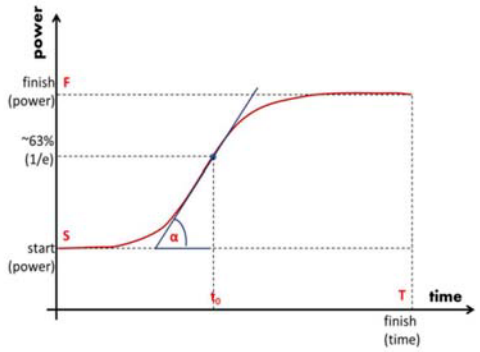


Figure 1. A special point of the Weibull function: the value, where t=t0 (1/e≈0.63). The derivative in the inflexion point equal (n/to)∙ (1/e)≈0.63*n, when to=1. The popular meaning of the parameters are: to is the stretching in x-direction (time-transformation), n is the stretching in y (incline of the curve). The parameters which has to be defined are the F, S, T, t0 and α, the finishing and starting power, the full treatment duration, the 63% of the power-increase and the slope of the power increase, respectively

The a-exponents were observed in various processes in wide range of applications. The generalized logistic function (sigmoid) could be constructed by various ways, but the so called Avrami-exponents (a, which is the exponent of the above Weibull function) are functionally appearing based on the extended works of FW. Cope [7], [8], there are some collected Avrami-exponents for various solid-state and biological processes show the universality of this logistic function.
The application of the Weibull distribution function approach multiple clinical applications and it is well established theoretically and practically, [9], [10], [11], [12]. It is used for a long time for survival description in gerontology [13], [14] and in oncology [15] as well.
The function has its inflexion point (where the tendency of decreasing changes) in t=t0 at 1/e (00.63) value. The derivative in this point is proportional to n. (The derivative there is exactly n/e [0-0.63n].) Therefore the parametric evaluation could be well checked in the t=t0 point. Note, the Weibull distribution could be well approached by normal (Gaussian) distribution over a>2. The area under the curve (shaded in the next figure) represents the complete energy-dose which is provided to the patient.

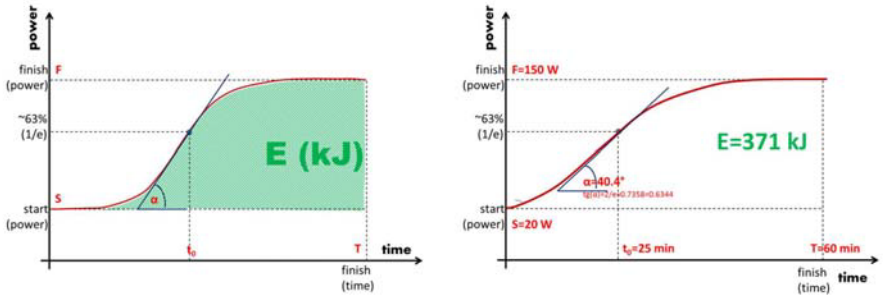


Figure 2. The provided energy is represented by the area under the curve (integral of the forwarded power, (a)), and the slope at the infexion point is proportional with the exponent "a", shown in numerical example (b)

However the continuous increase of the temperature does not fit to the homeostatic steady-state requests. Physiological response time (when the homeostatic equilibrium is reestablished after a definite disturbance) is 5-7 min. We propose at least 6 min on the definite chosen power level before the next increase step-up. Considering this transient as 6 min, the step-up heating is shown below. In this case the obtained dose is higher due to the upfitting rule, which we applied. In case of using 10 min relaxation time the protocol is shown on Figure 3.

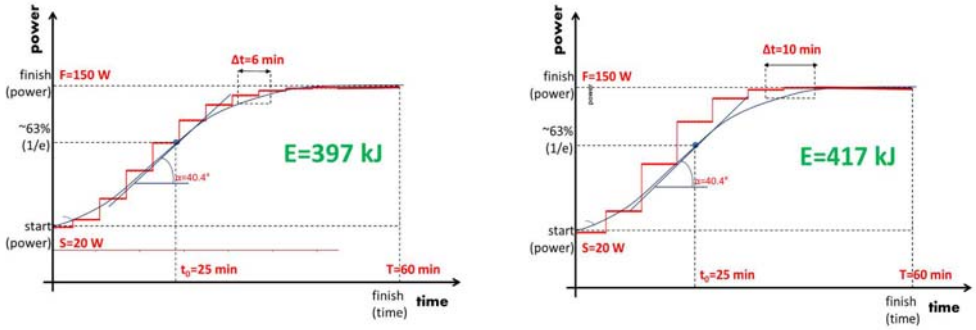


Figure 3. The step up heating follows the Weibull curve and keeps the steps until the homeostatic equilibrium. The provided cumulative energy could vary by the time-intervals of the steps

Difference between the poison and medicine is only the dose. In numerous cases people committed suicide taking medicine which would be useful in lower dosage in treatments. The dose is an important factor of efficacy safety and reproducibility too. In case of medication or radiation oncology we know the dose units as quantitative measurable values in mg/m2 or J/kg in chemo- or radiotherapies, respectively.
In hyperthermia the temperature is overemphasized as a dose, however it is not a quantitative parameter, it is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic average of the individual energies of the small units in the system. In chemotherapy the cytotoxic remedies could cease very serious side effects, their safety has emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.
When the medication definitely has no side effects (or the side effects are controlled) then the dose role has no upper limit by their safety, and also when the dose is limited but it is too high for the actual patient due to the biovariable poisoning limit, then the actually applied dose is of course lower, trying to fit it for the actual patient.
Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) sensing and note the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much actually it has to be modified by the personal requests. On the other hand, when the preset energy-dose is too small (the patients actually can tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety and together with this for the efficacy too.

Results

Oncothermia has formulated a new paradigm [16], and made a pioneering job: it was the modulated electric field application, which later had good continuation in the literature in many laboratories worldwide. Its definite breaking results were on the modulated field effect combined with the thermal actions [17], showing large development in the present clinical practice. The electric field action was considered in serious manner in 2000 by Nature [18], and has been intensively applied in the clinical practice [19], [20]. The modulated electric field actions were applied for various accepted clinical trials [21], [20].

The second new approach was the controlled micro-heating, [22], which makes it possible to introduce the dose as the absorbed power [23], [24]; like it is used in the standard radio-therapy as well.

The third new important field which was pioneered by oncothermia is the immune-stimulative applications of the modulated electric field, showing the definite natural apoptotic cell-killing [25], [26] with activation of various leucocytes [27] to isolate [28] and kill the malignant lesion. The fourth pioneering field is the [29] abscopal (bystander) effect of modulated electric field. According to the remark of world-famous tumor vaccination researchers in their last conference, it could be a good basis to be involved in this very modern and promising field. This effect makes a great opportunity to make the local treatment systemic [30], like the locally observed tumor becomes systemic by its malignant progress.

In clinical point of view Oncothermia makes also important and unique steps to go forward with proving its trustful performance [31]. It has various levels of clinical evidences, has multiple studies including phases of the data development from the toxicity measure (Phase I), [32],[33], through the efficacy (Phase II) [34], and the wide range clinical applications (Phase III/IV) [35]. Oncothermia has many retrospective studies but also many prospective ones in Phase II and Phase III categories. The retrospective data are compared to the large databases, and compared to the multiple clinical institutions, making statistical evidences of the validity of the data.

Presently altogether oncothermia has 54 clinical trials for malignant diseases involving 2796 patients from six countries (Germany, Hungary, Italy, S.Korea, China, Austria). These trials cover 15 localization (see Table 1.) The patients were in advanced stages, mostly over the 3rd line treatment. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)
Brain studies	10	521	73.99	22.19
Pancreasa studies	6	184	47.04	11.02
Lung studies	5	636	64.76	15.79
Bone	3	79		40.10
Liver metastasis	7	267	86.00	18.06
Colorectal	7	447		
Gynecology (pelvic)	5	100	93.22	33.25
Breast	1	103	97.10	52.10
Esophagus	2	19	41.70	55.64
Somach study	1	68	58.90	14.40
Kidney cancer	1	39	84.60	35.90
Urinary bladder cancer	1	18	85.00	36.50
Head and neck	1	64	92.20	26.10
Soft tissue sarcoma	1	16	100.00	35.90
Prostate	3	135	88.90	38.80
SUM	**54**	**2796**		

Table 1. List of oncothermia studies. Some references of various localizations: Bone (metastatic) [36], [37]; Breast [38]; Colorectal [39], [40], [41], [42], [43]; Gliomas [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], Esophagus [54]; Brain (metastatic) [55], Kidney [56]; Liver (primary) [57], Liver (metastatic) [58], [59]; Lung (NSCLC) [60], [61]; Lung (SCLC), [62], [59], Pancreas [63], [64], [65], [66].

Conclusion

Oncothermia has good clinical achievements in the clinical studies, making a stable basis of the clinical applications in various advanced primary and metastatic malignancies and giving the long time expected stable standard on oncological hyperthermia. Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes the accurate and personalized treatment possible by this method.

References

[1] Neber DW, Zhang G (2012) Personalized medicine: Temper Expectations, Science 337:910

[2] Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165

[3] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electrobiology 22 [4] Meggyeshazi N; Andocs G; Krenacs T. (2012) Modulated electro-hyperthermia induced programmed cell death in HT29 colorectal carcinoma xenograft, Virchows Arch (2012) 461 (Suppl 1):S131–S132 Prague, 8-12 September, 2012

[5] Hegyi G, Vincze G, Szasz A, (2012) On the dynamic equilibrium in homeostasis, Open Journal of Biophysics, 2:64-71

[6] Weibull W: A statistical distribution function of wide applicability, J. Appl. Mathematics, 18:293-297, 1951

[7] Cope FW: Detection of phase transitions and cooperative interactions by Avrami analysis of sigmoid biological time curves for muscle, nerve, growth, firefly, and infrared phosphorescence, of green leaves, melanin and cytochrome C, Physiol. Chem. And Phys, 9:443-459, 1977

[8] Cope FW: Solid State physical replacement of Hodgkin-Huxley theory. Phase transformation kinetics of axonal potassium conductance, Physiol. Chem. & Physics, 9:155-160, 1977

[9] Hajian-Tilaki KO, Hanley JA, Joseph L, Collet J-P: A Comparison of Parametric and Nonparametric Approaches to ROC Analysis of Quantitative Diagnostic Tests, Medical Decision Making 17:94-102, 1997

[10] Jones G. Rocke DM. Multivariate survival analysis with doubly-censored data: application to the assessment of Accutane treatment for fibrodysplasia ossificans progressive. Statistics in Medicine 21:2547-2562, 2002

[11] Avrami MA: Kinetics of phase change I-III, J. Chem. Phys. 7, 1103, 1939

[12] Wilson DL: The analysis of survival (mortality), data: fitting Gompertz, Weibull and logistic functions, Mech. Aging Dev. 74:15-33, 1994

[13] Piantanelli L: A mathematical model of survival kinetics. I. Theoretical basis, Arc. Gerontol. Geriatr. 5:107-118, 1986

[14] Economos AC: Rate of aging, rate of dying and the mechanism of mortality, Arc. Gerontol. Geriatr. 1:3-27, 1982

[15] Weston CL, Douglas C, Craft AW, Lewis IJ, Machin D; (on behalf of UKCCSG), (2004) British Journal of Cancer, 91:225-232

[16] Szasz A, Szasz O, Szasz N (2001) Electrohyperthermia: a new paradigm in cancer therapy. Wissenschaft & Forschung, Deutsche Zeitschrift für Onkologie, 33:91-99

[17] Andocs G, Renner H, Balogh L et al (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model. Strahlentherapie und Onkologie 185(2):120-126

[18] DePomerai D, Danniells C, David H et al (2000) Non-thermal heat-shock response to microwaves. Nature 405(6785):417-418

[19] Kirson ED, Schneiderman RS, Dbaly V, Tovarys F, Vymazal J, Itzhaki A, Mordechovich D, Gurvich Z, Shmueli E, Goldsher D, Wasserman Y, Palti Y (2009) Chemotherapeutic treatment efficacy and senditivity are increased by adjuvant alternating electric fields (TTFields). BMC Medical Physics 9:1-13

[20] Kirson ED, Dbal V, Rochlitz C, Tovary F, Salzberg M, Palti Y (2006) Treatment of locally advanced solid tumors using alternating electric fields (TTFields) - a translational study. Clinical Research 17: Phase II and III Adult Clinical Trials, Proc Amer Assoc Cancer Res, 47: #5259

[21] Zimmerman JW, Pennison MJ, Brezovich I, Yi N, Yang CT, Remaker R, Absher D, Myers RM, Kuster N, Costa FP, Barbault A, Pasche B (2011) Cancer cell proliferation is inhibited by specific modulation frequencies. British Journal of Cancer, pp. 1-7

[22] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electrobiology, 22:103-115

[23] Szasz A, Vincze Gy (2007) Dose concept of oncological hyperthermia: heat-equation considering the cell destruction. Journal of Cancer Research and Therapeutics, 2:171-181

[24] Szasz A (2007) Hyperthermia, a modality in the wings. Journal of Cancer Research and Therapeutics 3:55-66

[25] Andocs G, Meggyeshazi N (2010) Revealing the mechanism of action of modulated electrothermia experimentally in animal model (HT29 colorectal xenograft study. ESHO, Rotterdam, The Netherland, May 20-22

[26] Meggyeshazi N, Andocs G, Szasz A (2011) Possible immune-reactions with oncothermia. ESHO, Aarhus, Denmark, May 26-28.
[27] Saupe H (2010) Possible activation of neutrophiles by oncothermia. 1st International Oncothermia Symposium, Cologne, November 22-23
[28] Andocs G, Meggyeshazi N, Galfi P, Balogh L, Fonyad L, Muller L, Szasz O, Szasz A (2010) Experimental oncothermia in nude mice xenograft tumor models; 1st international Symposium of Oncothermia, Cologne, November 22-23, 2010
[29] Meggyeshazi N, Krenacs T, Szasz A (2010) Clinical studies and evidences of modulated RF conductive heating (oncothermia) method. 1st International Oncothermia Symposium. 22-23nd November 2010, Cologne, Germany
[30] Seong Min Yoon, Jung Suk Lee (2012) Case of Abscopal effect with Metastatic Non-Small-Cell Lung Cancer , Oncothermia Journal 5:53-57:103-115
[31] Szasz A et al (2005) Retrospective analysis of 1180 oncological patients treated by electro-hyperthermia in Hungary. Jahreskongress der Deutschen Gesellschaft für Radioonkologie, DEGRO 11, Karlsruhe, 26-29 May 2005
[32] Wismeth C et al (2009) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsing high-grade gliomas – Phase I clinical results. J.Neuro-oncology 98(3):395-405
[33] Wismeth C et al (2009) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsing high-grade gliomas – Phase I clinical results. Expanding the Frontiers of Thermal Biology, Medicine and Physics Annual Meeting of Society of Thermal Medicine, Tucson, USA, 3-7 April 2009y
[34] Sahinbas H, Baier JE, Groenemeyer DHW, Boecher E, Szasz A. (2006) Retrospective clinical study for advanced braingliomas by adjuvant oncothermia (electro-hyperthermia) treatment. www.gimtonline.de/uploads/media/Therapieergebnisse_Giloma_Studie_01.pdf
[35] Pang C (2012) Clinical Research on Integrative Treatment of Colon Carcinoma with Oncothermia and Clifford TCM Immune Booster, Oncothermia Journal, No.5
[36] Aydin H et al (2003) Strahlen-Hyperthermie bei Lebermetastasen und bei therapieresistenten Knochenmetastasen; Hyperthermia Symposium, Cologne, Germany, 25-26. October
[37] Bogovic J et al (2001) Posttreatment Histology and Microcirculation Status of Osteogenic Sarcoma after a Neoadjuvant Chemo- and Radiotherapy in Combination with Local Electromagnetic Hyperthermia; Onkologie 24:55—68
[38] Feyerabend T, Wioedeman GJ, Jaeger B et al (2001) Local hyperthermia, radiation, and chemotherapy in recurrent breast cancer is feasible and effective except for inflammatory disease, Int. J. Radiation Oncology Biol. Phys. 49:1317-1325
[39] Panagiotou P, Sosada M, Schering S, Kirchner H. (2005) Irinotecan plus Capecitabine with regional electrohyperthermia of the liver as second line therapy in patients with metastatic colorectal cancer; ESHO, Jun.8-11, Graz, Austria
[40] Fiorentini G, deGiorgi U, Turrisi G et al (2006) Deep electro-hyperthermia with radiofrequencies combined with thermoactive drugs in patients with liver metastases from colorectal cancer (CRC): a Phase II clinical study. ICACT 17th, Paris, France, Jan 30-Feb 2 2006
[41] Ferrari VD, De Ponti S, Valcamonico F et al (2007) Deep electro-hyperthermia (EHY) with or without thermo-active agents in patients with advanced hepatic cell carcinoma: phase II study. Journal of Clinical Oncology 25:18S, 15168
[42] Vigvary Z, Mako E, Dank M. (2002) Combined radiological and interventional treatment of non-operable rectal tumors and their liver metastases, Regional Radiology Conference, Maribor, Sept. 19-20, Slovenia
[43] Sahinbas H et al (2006) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas. Deutche Zeitschrifts fuer Onkologie 39:154-160
[44] Hager ED et al (2008) Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia. ASCO, Journal of Clinical Oncology, Annual Meeting Proceedings (Post-Meeting Edition) 26:2047
[45] Szasz A (2009) Brain glioma results by oncothermia, a review. Expanding the Frontiers of Thermal Biology, Medicine and Physics Annual Meeting of Society of Thermal Medicine, Tucson, USA, 3-7 April 2009
[46] Douwes F, Douwes O, Migeod F, Grote C, Bogovic J (2006) Hyperthermia in combination with ACNU chemotherapy in the treatment of recurrent glioblastoma, http://www klinikstgeorg.de/pdf/hyperthermia_in_combination_with_ACNU_chemotherapy_in_the_treatment_of_recurrent_glioblastoma.pdf
[47] Szasz A., Sahinbas H, Dani A (2004) Electro- hyperthermia for anaplastic astrocytoma and gliobastoma multiforme ICACT 2004, Paris, 9-12. February, 2004
[48] Fiorentini G, Giovanis P, Rossi S, Dentico P, Paola R, Turrisi G, Bernardeschi P (2006) A phase II clinical study on relapsed malignant gliomas treated with electro-hyperthermia, In Vivo. 20:721-724
[49] Hager ED (2004) Response and survival of patients with gliomas grade III/IV treated with RF capacitive-coupled hyperthermia, ICHO Congress, St. Louis USA
[50] Hager ED (2004) Clinical Response and Overall Survival of Patients with Recurrent Gliomas Grade III/IV Treated with RF Deep Hyperthermia – An Update, ICHS Conference, Shenzhen, China

[51] Sahinbas H, Szasz A (2005) Electrohyperthermia in brain tumors, Retrospective clinical study, Annual Meeting of Hungarian Oncology Society, Budapest November 3-5
[52] Renner H (2003) Simultane RadioThermoTherapie bzw.RadioChemoThermoTherapie, Hyperthermia Symposium, Cologne, Germany, October
[53] Sahinbas H, Grönemeyer DHW, Böcher E, Lange S (2004) Hyperthermia treatment of advanced relapsed gliomas and astrocytoma, The 9th International Congress on hyperthermic oncology, St. Louis, Missuri, ICHO, April 24-27
[54] Szasz A, Dani A, Varkonyi A (2004) Az elektro-hipertermia eredményei nagyszámú beteg retrospektív kiértékelésének tükrében Magyarországon. Magyar Klinikai Onkológiai Társaság III. Kongresszusa, Budapest, Hungary, 17-20 November 2004
[55] Ferrari VD et al (2007) Deep electro-hyperthermia (EHY) with or without thermo-active agents in patients with advanced hepatic cell carcinoma: phase II study. Journal of Clinical Oncology 25:18S-15168
[56] Hager ED et al (1999) Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Res 19(4C):3403-3408
[57] Szasz A (2009) Clinical studies evidences of modulated rf-conductive heating (mEHT) method. Paper presented at the 25th Annual Meeting of the European Society for Hyperthermic Oncology, ESHO, Verona, Italy, 4-6 June
[58] Dani A et al. (2004) Treatment of non-small-cell lung cancer by electro-hyperthermia. Strahlenbiologie und Medizinische Physik Deutscher Kongress für Radioonkologie, DEGRO, Erfurt 10-13 June 2004
[59] Dani A, Varkonyi A, Magyar T, Szasz A (2009) Clinical study for advanced pancreas cancer treated by oncothermia, Forum Hyperthermia, Forum Medizine, 2:13-19
[60] Dr. Seok Jun Haam (2010) Oncothermia treatment of lung carcinomas. 1st International Oncothermia Symposium, 22-23 November 2010 Cologne, Germany
[61] Doo Yun Lee, MD, Paik MD (2012) Complete Remission of SCLC with Chemotherapy and Oncothermia (Case Report). Oncothermia Journal 5:43-51
[62] Douwes F (2004) Thermo-Chemotherapie des fortgeschrittenen Pankreaskarzinoms. Ergebnisse einer klinischen Anwendungsstudie http://www.kstg.net/pdf/thermo-chemotherapie_des_fortgeschrittenen_pankreaskarzinoms.pdf
[63] Douwes F, Migeod F, Grote C (2006) Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und einer Zytostase mit Mitomycin- C und 5-Fluorouracil/Folinsäure.http://www.kstg net/pdf/pankreastherapien.pdf
[64] Renner H, Albrecht I (2007) Analyse der Überlebenszeiten von Patineten mit Pankreastumoren mit erfolgter kapazitativer Hyperthermiebehandlung, (Erstellt: Mr. Mirko Friedrich; May.2007) & STM
[65] Szasz A (2010) Oncothermia in gynecology. 25th Annual Meeting of Korean Society of Gynecologioc Oncology, 29-30. April 2010, Jeju, Korea
[66] Dani A, Varkonyi A, Magyar T, Szasz A (2010) A retrospective study of 1180 cancer patients treated by oncothermia. Forum Hyperthermia accepted (pp. 1-11)

Oncothermia Journal 7:318-321 (2013)

Deep temperature measurements in oncothermia processes

Gabor Nagy[1], Nora Meggyeshazi[3], Oliver Szasz[1,2]
(1) Oncotherm Kft., 2071-Paty, Ibolya u. 2., Hungary
(2) Department of Biotechnics, Szent Istvan University, 2100-Godollo, Pater K. u. 1., Hungary
(3) 1sr Department of Pathology and Experimental Cancer Research, Semmelweis University, 1085-Budapest, Ulloi ut 26., Hungary
Corresponding author: Gabor Nagy: nagygabor@oncotherm.org

Published: http://www.hindawi.com/cpis/medicine/2013/685264/

Deep temperature measurements in oncothermia processes

Abstract

Temperature in depth of in various model-systems was measured, starting with muscle and other phantoms. Temperature was measured by flouroptical system (Luxtron) in the various points of the phantoms. It was shown that the temperature can be selectively increased in the target. In water-protein phantom the protein coagulation (>60 °C) was observed selectively while the water temperature around it was a little higher than the room temperature.

Keywords: oncothermia, temperature, penetration-depth, hyperthermia, selectivity, phantom

Introduction

Research of oncothermia has wide range of temperature measurements from its origin in 1988. Numerous experiments were done in various model systems and phantoms, including various ex-vivo tissues and complex body-parts of various animals [1]. Independently from Oncotherm the temperature development was also measured in complex meat-phantom [2].

New model-experiments were performed recently to show the depth profile of heating and be sure on the deep heating facility by oncothermia devices. Some devices are using the size of the electrode pair for focusing, telling that the small electrodes have less penetration. It is true generally in the radiative approach, but our impedance heating is different. We had used the smallest available electrode (10 cm diameter) showing that even with this the impedance heating is effective in depth.

The problem of the controlled and focused heat-delivery to deep-seated tissues is a long-standing problem of the local hyperthermia in oncology, [3]. The multiple artificial methods to focus the temperature have numerous technical and physiological problems. The energy could be focused in a planned and accurate way, but the temperature spreads naturally. Further problem is the physiological control in living objects, which likely acts by negative feedback, limiting or blocking the temperature increase during the actual heating process.

Methods

The early (twenty years old) phantom measurements have been repeated under much more modern conditions, and have been checked with optical fiber thermo sensing method, and also the outside heating profile was controlled for visual pattern by a high-sensitivity thermo-camera system. The in-vivo models, as well as all the animal experiments, have used flouroptical temperature measurements in depth. The precise inserting of the sensors was controlled by imaging technologies in large animals and humans.

We had modeled various human sizes, [4], orienting waists [thickness] as: underweighted ~70 cm [~18 cm], healthy ~ 85 cm, [~21 cm] overweight ~114 cm, [~28 cm] obese ~152 cm [~33 cm] and used phantom thicknesses 15 – 32 cm depending on the patient's weight and the part of the body (see Figure 1.). The thickness of an average patient is around 22 cm. (see pictures below), so the asymmetric solution is better for humans than the symmetric. Probably there are many animals, (horses, cows, elephants, etc.) where the 22 cm is not enough, for these cases the symmetric solution is better. (We are using it in veterinarian solutions for these specialties).

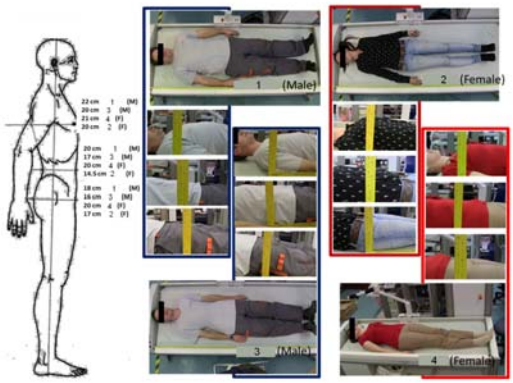


Figure 1. Typical human thicknesses of various healthy volunteers

First we measured in a 20cm phantom column, taking care on the heat-exchange with the environment and the cooling by the bolus and the water-bed. In the first experiment the phantom was mixed pork-meat taking care about the muscle and fat tissue combinations, modeling the living body complexity well. The phantom was a 10 cm diameter and 20 cm long cylinder, placed on the treatment bed, and heated by 60 W. (see Figure 2.) (20 cm was chosen for a thickness of an average suffering cancer patient.)

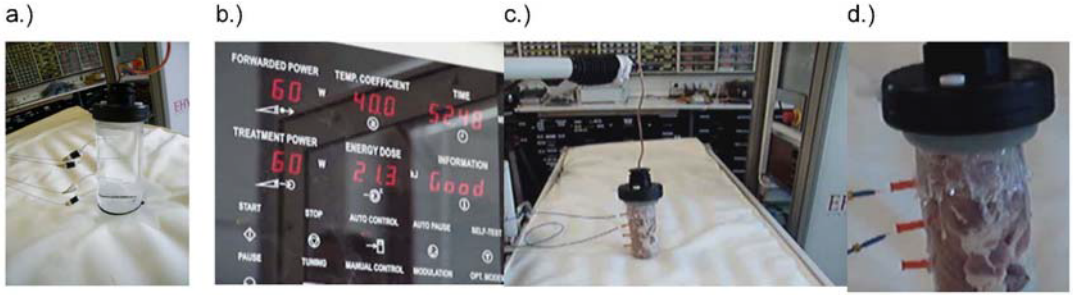


Figure 2. Typical experimental arrangement at EHY2000+ device. Experimental cylinder with the temperature sensors (a) Well turned device (b). The muscle phantom on the treatment bed (c) Muscle phantom with temperature sensors (d)

Other experiments were targeting the selection process of oncothermia. Various phantom materials were placed in distilled water and the system was treated by oncothermia, Figure 3.

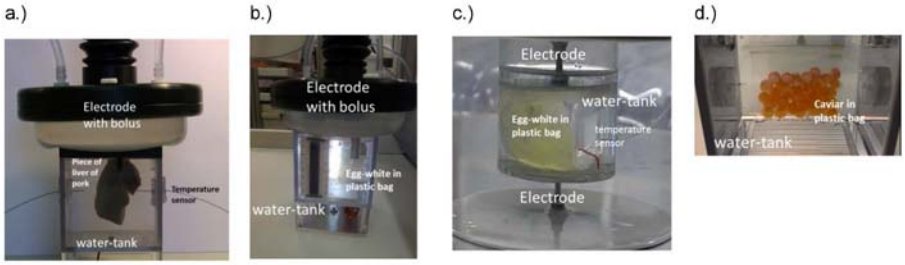


Figure 3. Various phantom arrangement for study the selection solutions. A piece of liver of pork (a), egg-white in rectangular water-tank (b), egg-white in cylindrical water-tank (c), caviar in water-tank (d)

Results

The deep temperature was rapidly enhancing, reaching the 42°C (from 24°C) increasing 18°C up, in the depth of 6 cm, (see Figure 4.).

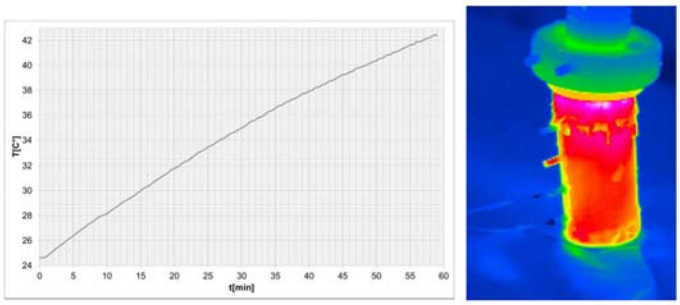


Figure 4. The temperature in depth was increased considerably. The outside temperature is of course lower, due to the cooling of the outside air on room temperature (22°C). The highest temperature in 6 cm depth (red temperature sensor in the thermo picture) was 42°C, which was reached from 25°C at start (17°C increase made by 60W, 60 min)

Approaching more the depth profile of the heating we measured the temperature in depths of 4, 8, 12, 16 cm depth. The same phantom system was used with chopped pork meat, (see Figure 5.) The power was 75 W. The measured temperatures were controlled by fluorooptical (Ipitek product) and thermistor sensors (Tateyama product). The starting initial temperature was 24°C. After 1 h the top sensor (4 cm depth) indicated over 54°C, while other depths of 8, 12 and 16 cm was developing 53°C, 51°C and 45°C. (The down electrode was cooled by the water-bed having much a loss of the heat. This temperature

development was 30°C the largest and 21°C the smallest values. Without water-bed the down-cooling was not effective, and the phantom was heated higher.

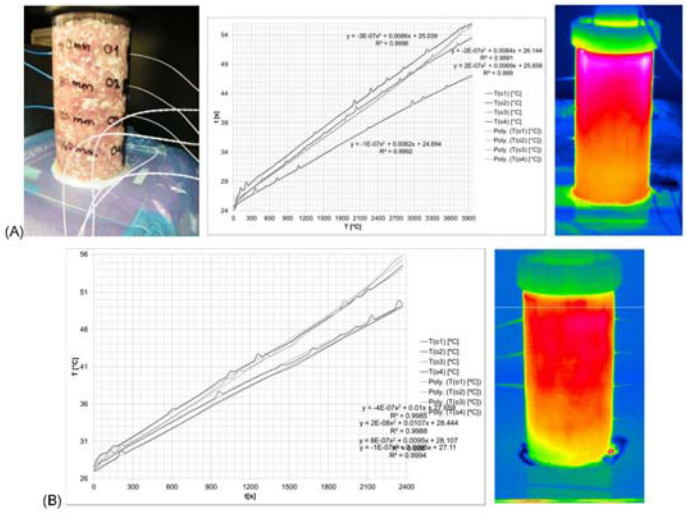


Figure 5. Depth profile with (A) and without (B) water-bed cooling effect. The temperature was about the same in both systems, when the heating time was 60 min and 40 min in the canse of water-bed and without water-bed cooling of the system. The deepest temperature however was over 45°C, (18°C increase) in 16 cm depth

The most realistic geometry was used when we put the experimental phantom 31 cm height, simulating an obese patient, (see Figure 6.). The in-depth measurements show definite increase of the temperature over 45°C (from 27°C) in depth of 24 cm applied 100 W heating power. The well increased temperature (peak) in depth of ~10 cm is well observable on the thermo picture.

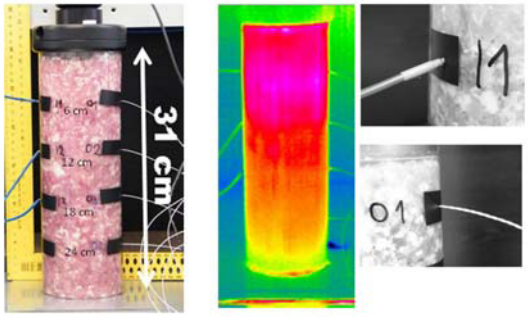
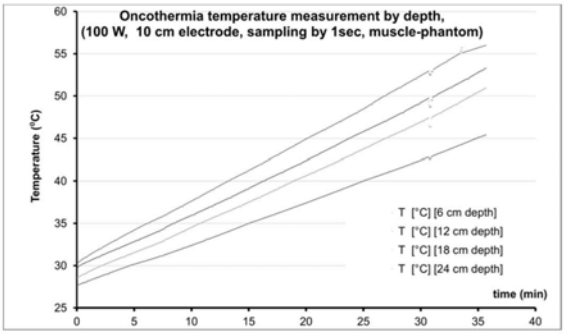


Figure 6. The phantom column, its thermo-picture during the treatment and the thermo sensors ("O" - Oncotherm-Tateyama system, "I" - Ipitek system for control). The thermo-picture shows a temperature distribution which has a maximum in depth of ~10 cm. The high temperature increase is proven in depth as much as 24 cm



The phantom experiments for demonstrating the selection process had shown well the selection mechanism of oncothermia. The liver experiment has shown a high temperature increase inside of the liver-piece, see Figure 7.

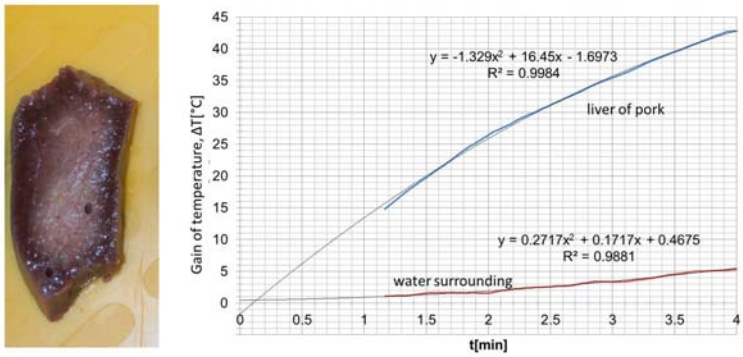


Figure 7.

The same selectivity was measured on egg-white in plastic bag surrounded with distilled water in two different-shape water-tanks (figure 8. and figure 9.). The temperature was as high as the protein coagulation happen (T>60 °C), while the water temperature was only slightly up (2°C over the room temperature 24°C), by the heat form the coagulated egg-white. The same was observed on the caviar phantom, when the balls were individually "cooked" without increase of the temperature of the surrounding water, see Figure 10.

Figure 8. Coagulation of egg-white starts in its inner-volume, while the water around remains cold

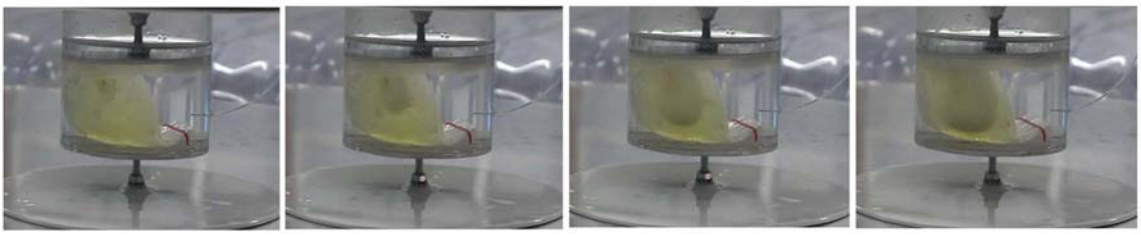


Figure 9. The development of the egg-white coagulaton is well seen in the cylindrical water-tank. The coagulation starts inside of the egg-white, the watr outside remains cold

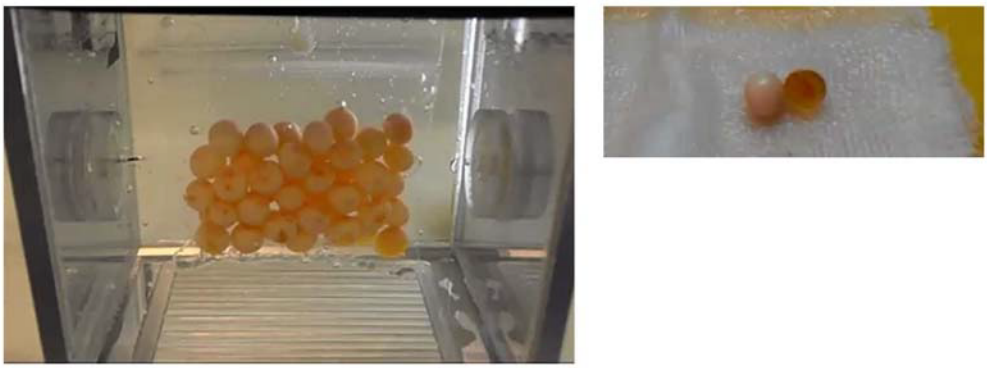


Figure 10. The caviar pieces are cooked, while the water had no temperature increase from room-temperature

Conclusion

Oncothermia is an effective deep heating method for tumor-lesions, increasing the temperature by a safe, controlled and well-targeted way. Phantom measurements proved the possibility of the selection when the local temperature can go up to ablative regime, without heating up the non-targeted volume. This is the basic of oncothermia selection and is expected to be effective in nanoscopic range at the membrane of the malignant cells.

Acknowledgement

Authors are thankful to Ms. E. Papp for her valuable assistance in the experiments.

References

[1] Szasz A., Szasz N., Szasz O. (2010) Oncothermia – Principles and Practices, Springer Verlag, Heidelberg, Dodtrecht

[2] Herzog A. (2008) Messung der Temperoturverteilung om Modell der nicht perfundierten Schweineleber bei lokoler Hyperthermie mit Kurzwellen mit 13,56 MHz; Forum Medizine, Forum Hyperthermie 1/10.2008:30-34

[3] Segenschmiedt M.H., et al. (1995) Thermoradiotherapy and Thermochemotherapy. Berlin, Springer-Verlag, vols. 1, 2.

[4] Khade S. (2012) Role of Non Surgical Treatments, Obesity., J Obes Wt Loss Ther 2:140. doi:10.4172/2165-7904.1000140

Oncothermia Journal 7:324-327 (2013)

Modulation effect in oncothermia

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]

(1) Department of Biotechnics, Szent Istvan University, 2100-Godollo, Pater K. u. 1., Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, 680-8553 Tottori, 4-101 Mnami, Koyama-Cho., Tottori Pref., Japan
(3) 1sr Department of Pathology and Experimental Cancer Research, Semmelweis University, 1085-Budapest, Ulloi ut 26., Hungary
Corresponding author: droliverszasz@gmail.com

Published: http://www.hindawi.com/cpis/medicine/2013/398678/

Modulation effect in oncothermia

Abstract

Conventional hyperthermia is based on the local or systemic heating, which is measured by the realized temperature in the process. Oncothermia applies nano-heating, which means high energy absorption in nanoscopic range of the malignant cell-membrane selectively. This high temperature and its consequent stress create special effects: it evolves possibility of chaperone proteins to be expressed on the outer membrane by softening the membrane, and starts various excitations for programmed cell-death of the targeted malignant cell. The process needs special delivery of the energy which selects as desired. A strict 13.56 MHz sinusoidal carrier frequency is amplitude modulated by time-fractal signals. The modulation is far from any sinus or other periodic patterns, it is a 1/f spectrum, having definite templates for its construction. In some personalized cases definite template is used for fractal pattern, which is copied from the actual character of the tumor-pathology or other specialty of the target.

Keywords: modulation, radiofrequency, hyperthermia, oncothermia, pink-noise, 1/f-spectrum, timefractal, apoptosis

Introduction

The understanding the principle of modulation starts with a simple everyday task: listening our favorite radiobroadcasts, like 107.1 MHz Cologne, 91.8 MHz Frankfurt, Radio Energy (Munich) 93.3 MHz etc. We choose the frequency (tune the radio to select it) and we enjoy the broadcast. The carrier frequency which was the basic of the tuning never meets the ear, it is too high for sensing, and anyway it would be a too monotonic sound, it is only a single frequency. Instead of monotony we hear the music or other information carried by this chosen frequency. The carrier-frequency delivers the real information coded in its modulation (see Figure 1.).

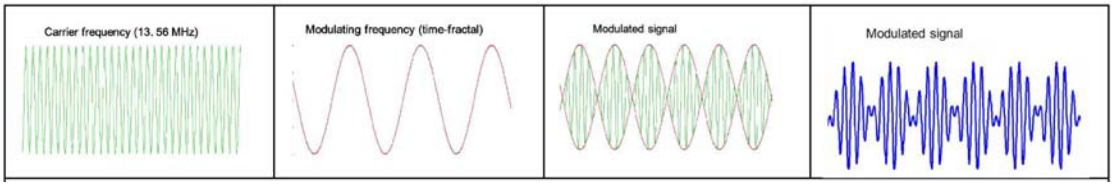


Figure 1. The amplitude modulation. Carrier frequency (a), modulation signal (b), modulated signal shown the frame of the modulator (c), modulated signal alone (d)

The carrier frequency carries two important information characters:
- its modulation finds the target on cellular level and
- its energy heats up the selected cells from outside by its neighboring extracellular matrix.

The modulation method is similar to the process when the light goes through the windows-glass. When the glass is transparent to that specific set of colors (visible light, definite interval offrequencies), its absorption is almost zero, all energy goes through it. However, when it has any bubbles, grains, precipitations, etc., those irregularities will absorb more part from the energy, their transparency will be locally low, their energy absorption will be high, they will be heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. The carrier frequency delivers the information (modulation frequencies), for which the cancer cells are much less "transparent" than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy.
The applied time-fractal modulation is one of the specialties, which only oncothermia has in hyperthermia applications in oncology.

Method

The living material is not an ordered solid. Contrary to the crystals, it is hard to introduce the cooperativity. The living matter is in aqueous solution, which is mostly well ordered, [1] in the living

state. This relative order formed the "dilute salted water" into the system having entirely different mechanical, chemical, physical, etc. behaviors as the normal aqueous solutions. Indeed, the important role in the living systems of the so called ordered water was pointed out in the middle of sixties, and later it was proven, [2]. At first the ordered water was suggested as much as 50 % of the total amount of the water in the living bodies [3]. The systematic investigations showed more ordered water [4], [5] than it was expected before. Probably the ordered water bound to the membrane is oriented (ordered) by the membrane potential, which probably decreases the order of the connected water, so increases the electric permeability of the water [6], and so decreases the cell-cell adhesion and could be the cause of the cell-division of even for the proliferation [6]. According to Warburg's effect the metabolism gradually favors the fermentation in malignancy [7]. The end-products of both the metabolic processes are ions in the aqua-based electrolyte. The oxidative cycle products dissociate like 6CO2+6H2O 9 12H+ + 6CO32- while the lactate produced by fermentation dissociates: 2CH3CHOHCOOH 9 2CH3CHOHCOO- + 2H+. Assuming the equal proton production (by more intensive fermentation energy-flux) the main difference is in the negative ions.

The complex lactate-ion concentration grows rapidly, and increases its osmotic pressure. Keep the pressure normal, the dissolvent (the monomer water) has to be increased as well, seeking to solvent by non-ordered water. Indeed, it is measured in various malignancies that the water changed to be disordered, [8], [9], [10], so in these cases the ordered water concentration in cancerous cells is smaller than in their healthy counterpart. Consequently, the hydrogen ionic transmitter became weak, the removal of the hydrogen ions became less active. This decreases the intracellular pH and the proton gradient in mitochondria, which is directly worsening the efficacy of ATP production. To compensate the lowered proton-gradient, the membrane potential of mitochondria grows. This lowers the permeability of the membrane, decreases the mitochondrial permeability transition, which have crucial role in apoptosis, [11], [12]. (The high mitochondrial membrane potential and low K-channel expression had been observed in cancerous processes, [13]). These processes lead to apoptosis resistance, and for the cell energizing the ATP production of the host cell (fermentation) became supported. The free-ion concentration increases in the cytoplasm, and so the HSP chaperone stress proteins start to be produced. This process needs more ATP as well as it is anti-apoptotic agent, so the process could lead to the complete block of apoptosis. Rearranging (disordering) the water structure needs energy [14]. It is similar to the way, like the ice is melted with latent heat from zero centigrade solid to liquid with unchanged temperature conditions. This drastic change (phase transition) modifies the physical properties (like the dielectric constant) of the material without changing the composition (only the microscopic ordering) of the medium itself.

The decisional role of the two metabolic pathways (the oxidative and the fermentative) was studied by Szent-Gyorgyi [6], having etiology approach, and using additional formulation. His interpretation describes the cellular states by two different stages. The alpha-state of the cell is the fermentative status.

What makes the difference on the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special "social" signals [15] commonly regulating and controlling their life. They are specialized for work-division in the organism, and their life-cycle is determined by the collective "decisions". The cancerous cells behave non-collectively; they are autonomic. They are "individual fighters", having no common control over them, only the available nutrients regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version, the cellular communications disappeared [16].

The problem of the autonomy of the malignant cells makes the treatment very much complicated, because cancer has its own fractal structure, [17]. The analysis of the fractal structures of malignancies could even indicate the stage of the disease [18]. Careful fractal analysis can make predictive information for the prognosis as well, [19].

Results

The effect of modulation was measured on immuno-deficient nude mice xenograft model made by HT29 human colorectal carcinoma cell-line. The single shot oncothermia was used for 30 min keeping 42 °C in the tumor. A day after oncothermia a definite difference can be detected between the modulated and unmodulated effects, which became very emphasized after two days, (see Figure 2. [20]). This is one of the reasons, why we propose in the protocols of oncothermia the treatment frequency every other day.

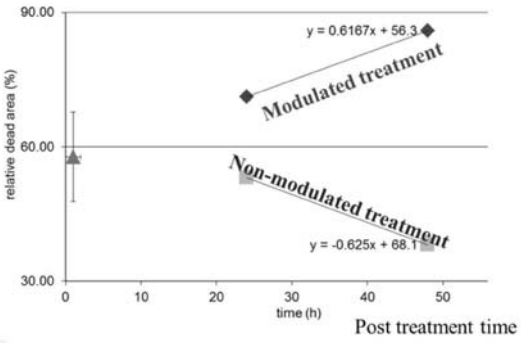


Figure 2. The modulation reestablsihes the apoptosis, the natural cell-killing process, and after 48 h the effect is obviously acting. (HT29 xenograft model on single-tumor-bearing mice, heating single shot, 30 min to 42 C. Animals were sacrificed 24 h after the treatment.)

The multiple fractal physiological proofs are extended by the oncothermia specialized experimental results too. We used the same xenograft model on a high number of nude mice (30 tumors were examined, 5-5 mice having double tumors in two arms, modulated (active) arm and non-modulated (passive arm)). The single shot experiment was also for 30 min, but the tumors were treated only on 40 °C. We know it from other experiments that this temperature is generally not enough to make hyperthermia effect in classical heating approach. The animals were sacrificed after 48 h, and the results (see Figure 3.) show well the modulation effect: the treated arm in modulated cases had 45.8% higher cell-distortion than the non-treated part, while the effect in the non-modulated mice was only 3,9%.

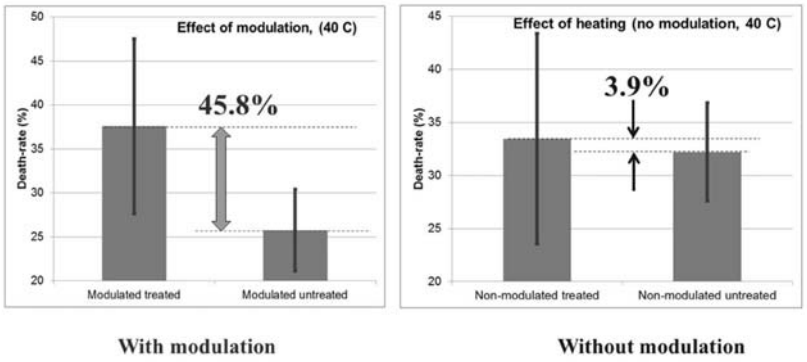


Figure 3. The modulation makes definitely and significantly higher tumor-destruction compared to the non-treated side than the non-modulated cases. (HT29 cell-line in nude mice, xenograft model, single shot for 30 min keeping at 40 C, 5-5 mice were used in both arms, sampling was taken 48 h after the treatment

More detailed explanation and background of the modulation applications in Oncothermia could be obtained from the Oncothermia book [21]. The modulation method has patent applications [22], [23], [24].

Conclusion

Oncothermia modulation is one of the three specialties of this treatment. Its efficacy and its role in the personalization process have introduced an effective tool for the apoptotic cancer-cell destruction.

References

[1] Cope FW (1969) Nuclear magnetic resonance evidence using D2O for structured water in muscle and brain. Biophys J 9(3):303-319
[2] Damadian R (1971) Tumor detection by nuclear magnetic resonance. Science 171(3976):1151-1153
[3] Cope FW (1975) A review of the applications of solid state physics concepts to biological systems. J. Biol. Phys. 3(1):1-41
[4] Hazlewood CF, Nichols BL, Chamberlain NF (1969) Evidence for the existence of a minimum of two phases of ordered water in skeletal muscle. Nature 222(195):747–750

[5] Hazlewood CF, Chang DC, Medina D et al (1972) Distinction between the Preneoplastic and Neoplastic State of Murine Mammary Glands. Proc Natl Acad Sci USA 69(6):1478-1480
[6] Szentgyorgyi, A.: The living state and cancer. Physiological Chemistry and Physics 12, 99-110 (1980)
[7] Warburg O (1966) Oxygen, The Creator of Differentiation, Biochemical Energetics, Academic Press, New York, 1966; (Warburg O: The Prime Cause and Prevention of Cancer, Revised lecture at the meeting of the Nobel-Laureates on June 30, 1966 at Lindau, Lake Constance, Germany)
[8] Gniadecka M, Nielsen OF, Wulf HC (2003) Water content and structure in malignant and benign skin tumors. Journal of Molecular Structure 661-662:405-410
[9] Beall PT et al (1979) Water-relaxation times of normal, preneoplastic, and malignant primary cell cultures of mouse mammary gland. In: 23rd Annual Meeting of the Biophysical Society, Atlanta, Georgia, USA, 26-28 February 1979
[10] Chung, S.H., Cerussi, A.E., Klifa, C., et. al.: In vivo water state measurements in breast cancer using broadband diffuse optical spectroscopy. Phys. Med. Biol. 53, 6713-6727 (2008)
[11] Fiskum G (2000) Mitochondrial participation in ischemic and traumatic neural cell death. Journal of Neurotrauma 17(10):843–855
[12] Ichas F, Mazat JP (1998) From calcium signaling to cell death: two conformations for the mitochondrial permeability transition pore. Switching from low- to high- conductance state. Biochimica et Biophysica Acta 1366:33–50
[13] Bonnet S, Archer SL, Allalunis-Turner J et al (2007) A Mitochondria-K+ Channel Axis Is Suppressed in Cancer and Its Normalization Promotes Apoptosis and Inhibits Cancer Growth. Cancer Cell 11(1):37–51
[14] Chidanbaram R, Ramanadham M (1991) Hydrogen bonding in biological molecules-an update. Physica B 174(1-4):300-305
[15] Raff MC (1992) Social controls on cell survival and death. Nature 356(6368):397-400
[16] Loewenstein WR, Kanno Y (1967) Intercellular communication and tissue growth. The Journal of Cell Biology 33(2):225-234
[17] Ballerini L Franzen L, Fractal Analysis of Microscopic Images of Breast Tissue, http://www.wseas.us/elibrary/ conferences/digest2003/papers/466-198.pdf (accessed Aug. 2012)
[18] Tambasco M, Magliocco AM, (2008) Relationship between tumor grade and computed architectural complexity in breast cancer specimens, Human Pathology, 39:740-746
[19] Delides et al (2005) Fractal Dimension as a Prognostic Factor for Laryngeal Carcinoma. Anticancer Research 25: 2141-2144
[20] Andocs G. (2008-2009) Unpublished experiments for oncothermia know-how
[21] Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and Practices, Springer, Heidelberg
[22] Szasz A, Szasz N, Szasz O (2009) Radiofrequency hyperthermia device with target feedback signal modulation. European Patent Application No. EP 08075820.4
[23] Szasz A, Szasz N, Szasz O (2011) Device and procedure for measuring and examining the signal of systems releasing measurable signals during operation or in response to external excitation. European Patent Application No. EP 05798498.1
[24] Szasz A, Szasz N, Szasz O (2012) Fractal templates and fractal feedback in homeostatic control. European Patent Application (pending)

Oncothermia Journal 7:329-332 (2013)

Synergy between TCM and Oncothermia

Hegyi Gabriella[1]
(1) Pecs University, Health Science Faculty, Hungary, CAM department

Synergy between TCM and Oncothermia

TCM and cancer

Traditional Chinese medicine-based herbal medicines have gained increasing acceptance worldwide in recent years and are being pursued by pharmaceutical companies as rich resources for newer drug discovery. For many years, traditional Chinese medicines (TCM) have been applied for the treatment of cancers in China and beyond. Chinese medicine employed treatments for cancer for over two millennia. The book The Rites of the Zhou Dynasty (1100- 400 BCE) refers to physicians specializing in the treatment of swellings and ulcerations or necrosis and ulcerations. These terms are still utilized in the modern practice of traditional Chinese medicine to denote the study and treatment of tumors that are both benign and malignant.8 Early Chinese medical texts described different types of breast tumors and discussed their clinical appearance, physiological origin and severity. Over 100 names were recorded for tumors in early medical literature. Most of these terms represent conditions that would be regarded as early cancerous conditions in the Western medical literature. The most frequently cited term for breast cancer was breast rock12. In the Yellow Emperors Classic of Internal Medicine (written circa 250 BCE), the first clinical picture of breast cancer was described. The prognosis was estimated to be approximately ten years after diagnosis and the process of progression, metastasis and death was detailed.

The current trend in China is to integrate, or combine Western therapies with TCM in the treatment of cancer. There are no available statistics on the proportion of women using this approach. Our collaborators in China- Hebei University TCM Department- estimate that about 70%-80% of women diagnosed with breast cancer in the metropolitan areas, where Western medicine (WM) is favoured, are using the combined approach at some point during their treatment of breast cancer while a very small fraction of women use TCM as a sole therapy. The treatments employed by the TCM physicians are aimed at controlling side effects and toxicities attributed to cancer therapies, improving quality of life, preventing recurrence and prolonging survival.

Herbal medicines are generally low in cost, plentiful, and show very little toxicity or side effects in clinical practice. However, despite the vast interest and ever-increasing demand, the absence of strong evidence-based research and the lack of standardization of the herbal products are the main obstacles toward the globalization of TCM. In recent years, TCM research has greatly accelerated with the advancement of analytical technologies and methodologies (1). Cancerous conditions are well-known in the traditional Chinese medical system. In the classics of TCM, “Huang Di Nei Jing Di” (黃帝內經) published more than 2000 years ago, there are descriptions of the pathogenesis, appearances and treatment principles of tumors (瘤), such as muscle, tendon and bone carcinomas; however, this term does not differentiate between malignant and nonmalignant tumors. It was not until the Sung Dynasty (ca. 1300 AD) that the first reference to cancer - the Chinese word Ai (癌) meaning malignant carcinoma - first appeared in the ancient medical book “Wei Ji Bao Shu” (衛濟寶書). According to the theories of TCM, cancer is caused by imbalances between endogenous physical conditions of the body and exogenous pathogenic factors. The internal condition of the body plays a dominant role in the onset of cancer. In other words, factors can induce cancer only when the body's own defense system fails. Those pathogenic factors, in Chinese medicine terms, include accumulated toxins, “heat” and blood stasis, and they attack when a person is in a weak physical condition, without the strength to resist. Furthermore, malfunction of the body-mind communication network may also trigger the development of cancer (2) So, TCM expert doctors view cancer as a systemic disease associated with the state of the whole body (or disturbance of the signaling network, to use a modern term). “Systemic” in the TCM doctors' views, means “state of the whole body”. “Cancer is the manifestation of a breakdown in the body's ability to handle pathogenic factors, not a local disease of cells or organs.” Accordingly, the treatment philosophy and strategy of TCM emphasizes holistic modulation and improvement of the whole body rather than removing the tumor mass or killing the cancerous cells. This treatment strategy is particularly enforced for cancer patients at the late stages. In these stages, the focus of treatment is extending the life expectancy and improving the quality of life of the patient; in other words, the focus is on the patient not the tumor mass (帶瘤生存).The other major principle of TCM is the emphasis on an individual therapy. For the same type of cancer in different persons, the diagnosis and treatment schemes could be very different. This is called the principle of “treatment based on symptom pattern differentiation (辨證論治)”. In other words, TCM expert doctors make the diagnosis and prepare a treatment scheme based on the assessment of the pattern of symptoms manifest in each individual. When herbs are called for, most commonly, several are used together, and the whole herbs are used, not purified compounds. Thus, in the

prescription, there will be multiple effective components delivering a comprehensive, integrated treatment of cancer through multiple targets and their associated pathways. This approach is in line with the view of TCM that cancer is a systemic disease that requires a holistic approach and medicines that can produce therapeutic actions through multiple targets. While this approach differs from that of conventional medicine, the effects of treatment still come down to biochemistry. If treatments are effective, then there must be underlying mechanisms that can be investigated and verified scientifically. Understanding these mechanisms can help us expand the efficacy of both Western and Chinese medicines in a logical, rational way.

Future Prospect of TCM Herbal Medicines in Cancer Research

The cellular and animal studies have provided strong molecular evidences for the anticancer activities of the TCM herbal medicines, tested as pure compounds or as crude extracts of the single herbs or the complex formulas. However, several important questions remain to be answered. Do TCM-derived herbal medicines possess any special effects other than those often seen with conventional drugs for cancer treatment? There has been little investigation to make a side-by-side comparison. An earlier work was conducted on the anticancer effects of protodioscine (glycosides) from the rhizome of Dioscorea collettii var. hypoglauca, a Chinese herbal remedy for the treatment of cervical carcinoma, carcinoma of urinary bladder and renal tumor for centuries, against a 60 NCI human cancer panel (3), and it was found to be specifically effective for cervical carcinoma, bladder and renal cancer cell lines. Moreover, based on an analysis of the COMPARE computer program with protodioscin as a seed compound, no other compounds in the NCI's anticancer drug screen database have a cytotoxicity pattern (mean graphs) similar to those of protodioscin, indicating that a potential novel mechanism of anti-cancer action is involved. This may be one of many methods by which the unique properties of TCM can be revealed in a concise manner. The other question to be addressed in the future is whether the methodologies and the in vitro and in vivo biological models currently employed to investigate the therapeutic nature of traditional Chinese medicines are good enough. By now 66 herbs are known that have been used for anticancer studies all over the world. They were grouped these herbal plants into seven functional groups based on the traditional usage for cancer treatment. Interestingly only a small subset of herbs is considered toxic, grouped under the category of "medicinal with cytotoxic function", the majority is not. On the other hand, the majority of TCM-derived components shown above are in the same category as the conventional anticancer drugs which induce apoptosis. In a previous study (4), we used a cell system by which the inhibitory effects of non-cytotoxic chemicals were assessed by a focus formation assay upon transfection of ras oncogene to the host cells. Using this system, two well-studied medicinal mushrooms Ganoderma lucidum and Tricholoma lobayense with anticancer potential were examined for their possible adverse effects on cell transformation induced by ras oncogene. The results indicated that both species of mushrooms strongly inhibited ras-induced cell transformation. However, the inhibitory effect of the mushroom extracts was not due to a direct killing of the transformed cells; rather, it seems to have been mediated through the surrounding normal cells. This normal cell-dependent growth inhibitory effect is also observed with oleanolic acid isolated from Oldenlandia diffusa (5). These examples suggest that, at least some, TCM medicines exert their anticancer effects through mechanism(s) other than apoptosis. Looking forward, we have to see three specific issues that will require focused more attention:

(i) more well-designed clinical trials are required to support the effectiveness and the safety of TCM in the management of cancers/ applying together modern technology as oncothermia;

(ii) new parameters based on the unique properties and theory of TCM are needed to assess the clinical efficacy of TCM in clinical trials; and

(iii) new approaches to research may be needed, given the nature of TCM herbs as being fundamentally different from drugs. There is evidence that the reductionist approach, i.e., searching for one or a few active ingredients in an herb or formula, may not elucidate the efficacy of herbal medicines; a systems biology approach may be more appropriate and productive, in terms of developing effective treatment protocols.

Undoubtedly, the evaluation of the therapeutic effects and the benefits of TCM therapy for cancer patients is a significantly complex, albeit significant issue. TCM therapy, based on multiple medicinal herbs and an holistic approach to diagnosis as well as treatment, means that a clinical study of TCM treatment is more difficult and complicated than the study of single compound drugs. In addition to the conventional "standards" used for WM (western medicine) clinical trail, there is a need to develop a set of parameters

that are suitable to the assessment of TCM therapy. The effects, as well as the toxicity, of individual herbs or, especially, of single compounds derived from the herb cannot completely reflect the benefits and toxicity of the herbal combination. When whole herbs are not studied, improper or biased results and conclusions might be unavoidable (6). As a goal, to develop and involve TCM into rational cancer therapy together spin-off technology oncothermia, more well-designed intensive clinical evaluations and translational laboratory studies are absolutely needed. And, close collaboration between TCM and conventional Western medicine professions and a combination of TCM with modern multidisciplinary cutting-edge technologies like oncothermia, such as omic methodology on systems biology (7), would provide us with an attractive and effective strategy to achieve this goal for benefit patients.

Anti-cancer effects and underlying mechanisms of TCM – derived complex formulas – really a "great chellenge"

There are only a few mechanistic studies on the action of TCM formulas as anticancer agents. One study was on San-Zhong-Kui-Jian-Tang (8), a complex formula comprising 17 different herbs, which is used for cancer therapy in China. It was found to induce the mitochondrial apoptotic pathway by changing Bax/Bcl-2 ratios, cytochrome c release and caspase-9 activation, but did not act on Fas/Fas ligand pathways in two human breast cancer cell lines, MCF-7 and MDA-MB-231. A similar study was carried out by the same laboratory (9) on Huang-lian-jie-du-tang (HLJDT) known to possess anti-inflammatory activity. The in vitro study conducted in two human liver cancer cell lines, HepG2 and PLC/PRF/5, found that HLJDT caused cell arrest by up-regulating the inactive form of Cdc2 and Cdc25, and down regulating the levels of Bcl-2 and Bcl-XL.[1] Furthermore, HLJDT increased the ratio of Bax and Bak/Bcl-2 and Bcl-XL[2] and the associated cell survival pathways, and subsequently triggered the mitochondrial apoptotic pathway. It was the collective actions of the herbs in the formula that were inhibiting the growth of cancer cells tested both in vitro cell lines and in vivo in nude mice. Another study is the study of a classic formula, Guizhi-fuling decoction (GZFLD) (10). The formulation consists of five herbs: Cinnamomum cassia, Paeonia lactiflora, Paeonia suffruticosa, Poria cocos, and Prunus persica. Accordingly, GZFLD inhibited the growth of HeLa cells by activating the tissue inhibitor of metallo-peptidases (TIMPs) and causing the suppression of the activity of the matrix metallo-peptidase (MMPs) that play a key role in the degradation of the extracellular matrix and promotion of cell proliferation.

[1] BCL2: B cell leukemia/lymphoma 2, BCL-XL: B cell leukemia/lymphoma x
[2] MCL-1: myeloid cell leukemia sequence, 1MDM2: murine double minute 2

In the same study, GZFLD was also shown to inhibit tumor growth and angiogenesis in an in vivo animal model. Another report (11) concerned a classic formula "bojung-bang-dock--tang (BJBDT)" consisting of Astragalus membranaceus Bunge, Atractylodes japonica Koidzumi, Coiz lacryma-jobi Linne var. ma-yuen stapf, Dioscorea batatas Decaisne, Dolichos lablab Linne, Panax ginseng C. A. Mey, Polygonatum sibiricum Delar. ex Pedouté, Poria cocos (Schw.) Wolf. Two related studies (12, 13) found that BJBDT demonstrated anti-angiogenesis by blocking VEGF/VEGFR[3] activities in human umbilical vein endothelial cells. Interestingly, BJBDT can prevent cisplatin-induced toxicity and apoptosis in normal MCF-10A, but not in MCF-7 and MDA MB-231 breast cancer cells, suggesting the herbal formula can be applied as a cancer chemopreventive agent (14). The synergistic effects of herbs in a TCM formula were well illustrated in a new study, in which a TCM-based formula, Realgar-indigo naturalis (RIF), was applied in the treatment of acute promyelocytic leukemia (APL). The RIF formula has three components, realgar, indigo naturalis, and Salvia miltiorrhiza of which tetra-arsenic tetrasulfide, indirubin, and tanshinone IIA, respectively, are the major active ingredients. The study demonstrated that tetraarsenic tetrasulfide is the principle component of the formula, while tanshinone IIA and indirubin are the adjuvant ingredients. Together these herbs have shown a synergistic action against APL effective in both in vitro and human clinical studies.

Literature

1. W. L. Wendy Hsiao Liang Liu. The Role of Traditional Chinese Herbal Medicines in Cancer Therapy - from TCM Theory, Planta Med 2010; 76(11): 1118-1131
2. Macek C. East meets West to balance immunologic yin and yang. JAMA 1984; 251 433-435 439
3. Hu K, Yao X. Protodioscin (NSC-698 796) : its spectrum of cytotoxicity against sixty human cancer sell lines in an anticancer drug screen panel, Planta Med 2002; 68: 297-301

4. Hsiao W L, Li Y Q, Lee T L, Li N, You M M, Chang S T. Medical mushroom exacts inhibit ras-induced cell transformation and the inhibitory effect requires the presence of normal cells. Carcinogenesis 2004; 25: 1177-1183
5. Wu P K, Chi Shing Tai W, Liang Z T, Zhao Z Z, Hsiao W L. Oleanolic acid isolated from Oldenlandia diffusa exhibits a uique growth inhibitory effects against ras-transformed fibroblasts. Life Sci 2009; 85: 113-121
6. Chiu J, Yau T, Epstein R J. Complication of traditional Chinese/Herbal medicines (TCM)- a guide for perplexed oncologists and other cancer caregivers. Support Care Cancer 2009; 17: 231-240
7. Efferth T, Li P C, Konkimalla V S, Kaina B. From Traditional Chinese Medicine to rational cancer therapy. Trends Mol Med 2007; 13: 353-361
8. Hsu Y L, Yen M H, Kuo P L, Cho C Y, Huang Y T, Tseng C J, Lee J P, Lin C C. San-ZHong-Kui JIan-Tang, a traditional Chinese medicine prescription, inhibits the proliferation of human breat cancer cell by blocking cell progression and inducing apotosis. Biol Pharm Bull 2006; 29: 2388-2394
9. Hsu Y L, Kuo P L, Tzeng T F, Sung S C, Yen M H, Lin L T, Lin C C. Huang-lian-jie-du-tang, a traditional Chinese prescription, induce cell-cycle arrest and apoptosis in human liver cancer cells in vitro and in vivo. J Gastroenterol Hepatol 2008; 23: e290-e299
10. Yao Z, Shulan Z. Inhibition effect of Guizhi-Fuling decoction on the invasion of human cercical cancer. J Ethnopharmacol 2008; 120: 25-35
11. Kang S, Jeong S, Kwon H, Yun S, Kim J, Lee H, Lee E, Ahn K S, Kim S. Protective effect of Bojungbangdocktang on cisplatin induced cytotoxicity and apoptosis in MCF-10A breat endothelian cells. Environ Toxicol Pharmacol 2009; 28: 430-438
12. Lee H J, Kim K H, Jang Y S. Protective effect of ethanol extract of Bojungbangdocktang on cisplatin induced cytotoxicity. J Oriental Pathol 2007; 21: 1-5
13. Jang Y S, Lee H J, Lee H J, Kim K H, Won S H, Lee J D, Ahn K S, Kim J H, Yu Y B, Kim S H. Bojungbangdocktang inhibits vascular endothelial growth factor induced angiogenesis via blocking the VEGF/VEGFR2 signaling pathway in human umbilical vein endothelial cells. Chin Sci Bull 2009; 54: 227-233
14. Wang L, Zhou G B, Liu P, Song J H, Liang Y, Yan X J, Xu F, Wang B S, Mao J H, Shen Z X, Chen S J, Chen Z. Dissection of mechanisms of Chinese medicine formula REALGAR-Indigo naturalis as an effective treatment for promyelocytic leukaemia. Proc Natl Acad Sci U S A 2008; 105: 4826-4831

[3] VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor

Introduction of the international quality management systems by sample of Oncotherm Group

Anett Gallne-Valyi[1]
(1) Oncotherm Kft., 2071-Paty, Ibolya u. 2., Hungary
E-mail address: gallnevalyianett@oncotherm.org

Introduction: The most important aspect for the Oncotherm Group is that our medical devices are prepared according to the concerning international standards and fulfill the inquiries of our customers.
These standards are the followings:
_ ISO 9001:2008 Quality Management Systems. Requirements
_ ISO 13485:2003/AC:2009 Medical Devices. Quality Management Systems. Requirements for regulatory purposes
_ 93/42/EEC MDD (Medical Device Directive)

Method: I would like to introduce the organizational structure and processes of Oncotherm Group and the requirements which should be adapted (see above).
The Oncotherm Group consists of two parts: the Oncotherm Kft., which is in Hungary and the Oncotherm GmbH, which is in Germany, but these two firms are one unity.
They are working together and they have got common quality management systems.
The research, design and development, and the manufacturing are in Hungary, but the marketing, sales, costumer service and service activities are in Germany, so these two parts create one well operative company. The Company-Group is a marketing method (Oncothermia Method, OTM) which is in synergy with the devices (Oncothermia Device, OTD) and integratively presented on the market as Oncothermia System (OTS). This unification of the German medical and constructive knowledge with the general European manufacturing culture is based on European Medical Device Directive and ISO standards. We do everything in Europe and are proud on that high level production culture which is represented by our 21 years old company.

Summary: Our devices are prepared by team-working of Hungarian and German highly qualified specialists, and there is more than 20 years hard work, experience and knowledge behind the OncoTherm System, which are the basis of our recent approval by TÜV Süd Product Service GmbH.

Oncothermia Journal 7:335-336 (2013)

Production support by LabView-based data-acquisition systems

Gabor Skrihar[1]
(1) Oncotherm Kft. 2071-Paty, Ibolya u. 2.., Hungary
skrihargabor@oncotherm.org

Production support by LabView-based data-acquisition systems

Abstract

Medical devices are complex products requesting high level of safety and reliability because of their sophisticated functions. Automation of the quality control and the visualization of the steps of the production processes are useful supports of the production process. Our objective is to show a way of production support by LabView system.

Introduction

During the production of a product a lot of tests and measurements are done. First the electronic boards are checked separately, then the modules which are built from them are tested separately, and finally a lot of tests are conducted on the assembled system. During these test a lot of data could be acquired from the product, but – especially at the final testing of the product – the data acquisition could be difficult, because:

• The testing time is so long, that the continuous observation of the test is not possible
• If during the measurement more instruments are used, the simultaneous and continuous observation of all of them is not possible.
• Most of the measuring devices don't provide built-in data acquisition and storage
• Although some instruments have this function, it could be difficult to synchronize the data acquired by various instruments.

The solution of these problems is such a data collection system, that in real-time collects and synchronizes all of the information, that the used instruments provide during the actual measurement and then stores them into a common database, allowing the common processing of them. By this way the efficiency of the production could be greatly increased. For us at Oncotherm it is a priority to increase both the speed and the quality of the production of our products, so we started to develop integrated data-acquisition systems to support our production tasks.

Discussion

The main element of these systems is the LabView program suite, which has been developed especially for data-acquisition and instrument control and is provided by National Instruments. It can be used for a wide range of sophisticated tasks as watermonitoring [1], control of imaging [2], or bio-signals [3], even virtual laboratories can be constructed [4].

We know the LabView application is suitable for RF-controlling processes [5] and for complicated production as well [6]. Our objective is to support a production of the radio-frequency operating medical treatment device [7].

The main task of LabView is to control the NI's own DA units, but the products of the most important instrument manufacturers are controllable with the suite too. During our projects we use both NI instruments and the instruments of other manufacturers (Tektronix, Rhode&Schwartz) too.

One of our main ambitions is to monitor of the manufactured EHY-2000 oncothermia devices during their final tests, which means lots of test treatments continuously day and night. During these test treatments important data can be collected about the general behavior and the reliability of the system, which are the key factors concerning the quality of the product.

The device sends important information about its state by RS232 serial port and the inner signal lines of the device are monitored by NI data-acquisition devices.

A typical data acquisition system consists of the following instruments and provides us the following information:

• EHY-2000:
• By serial port: time after the start of the treatment, output power, reflected power and the states of the various protection signal lines
• By direct monitoring of signal lines: the control voltage of the amplifier and the voltages proportional with the forwarded and reflected power.
• R&S RF power meter: used as an external reference for the accuracy of the power measurement of the device.

• Multimeter: used as a current meter to monitor the correct consumption of the amplifier.
By using the data provided by the reviewed instrumentation we can get a clear picture of the energetic efficiency and the general behavior of the amplifier, which
– as the most difficult part of the device – needs the most testing.
Of course, the data-collecting systems always follow the demands of the current projects, capitalizing the flexibility of the LabView-based DA systems. On the bases of our experiences until now we have more ways of improvement in this field. The most important ones are:
• Research support: integrated data acquisition during laboratory experiments, focusing to collect data from the Lab-EHY laboratory device and the 4-channel thermometer also developed by Oncotherm.
• Production support: automated testing of our products by LabView-based instrumentations

Conclusion

The LabView based production and quality control of the RF-operating medical device are feasible. By realizing this conception we can both improve the quality of our products and the affectivity and the speed of our R&D projects, so we are committed towards these ways.

References

[1] L.Wiliem, D.Hargreaves (2008) Identification of Critical Criteria of On-line Data Acquisition system, Asian International Journal of Science and Technology in Production and Manufacturing Engineering, 1(2), pp. 11-16.

[2] Bify Baby Abraham, A. Anitha (2012) Designing of Lab View Based Electrical Capacitance Tomography System for the Imaging of Bone Using NI ELVIS and NI USB DAQ 6009, Bonfring International Journal of Power Systems and Integrated Circuits, Vol. 2, 2. Pp. 1-6

[3] P. C. D'Mello, S. D'Souza (2012) Design and development of a Virtual Instrument for Bio-signal Acquisition and processing using LabVIEW, International Journal of Advanced Research in Electrical, Electronics and Instrumentation Engineering, Vol. 1, Issue 1, July 2012

[4] N. Ertugrul (1999) Towards Virtual Laboratories:a Survey of LabVIEW-based Teaching/Learning Tools and Future Trends, The Special Issue on Applications of LabVIEW in Engineering Education, International Journal of Engineering Education, No. 16, Vol. 3, p.p. 171-179.

[5] Joseph P. Ozelis, Roger Nehring (2007) RF and data aquisition systems for Fermilab's IRC SRFcavity vertical test stand, Conference: IEEE Particle Accelerator Conference, Albuquerque, NM, 25-30 June 2007

[6] J. Lee, J. Zhang, N. Zheng, X. Li (2012) The process control system based on LabVIEW in a hardening die steel production line, (ICIA) 2012 International Conference on Information and Automation, 6-8 June 2012

[7] Szasz A, Szasz O, Szasz N: Physical background and technical realizations of hyperthermia, in: Hyperthermia in cancer treatment: A primer, Baronzio GF, Hager ED (Eds), Springer Science, New York, 2006 Ch.3, pp.27-59

[8] G. Polaków, M. Metzger (2007) Agent–Based Approach for LabVIEW Developed Distributed Control Systems, Proceeding KES-AMSTA '07 Proceedings of the 1st KES International Symposium on Agent and Multi- Agent Systems: Technologies and Applications, Pages 21 - 30

Oncothermia Journal 7:338-341 (2013)

Hyperthermia vervus Oncothermia: cellular effects in cancer therapy

Gyula P Szigeti[2], Gabriella Hegyi[3], Oliver Szasz[1]

(1) Department of Biotechnics, St. Istvan University, 2103-Godollo, Pater K. u. 1., Hungary
(2) Department of Physiology, University of Debrecen, Hungary and Insitute of Human Physiology and Clinical Experimental Research, Semmelweis University, 1094-Budapest, Tuzolto u. 37-47, Hungary
(3) Department of Complementary and Alternative Medicine, University of Pecs, 7621-Pecs, Vorosmarty u. 4., Hungary
Corresponding author: szigeti.gyulapeter@gmail.com

Published: http://www.hindawi.com/cpis/medicine/2013/274687/

Hyperthermia versus Oncothermia: cellular effects in cancer therapy

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 >42.5oC 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 CO2 partial pressures,
5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
6. an inhibition of the Na+/H+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+ 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.

Acknowledgement

Authors acknowledge the experimental work and fruitful discussions of Dr. Nora Meggyeshazi and Dr. Gabor Andocs.

References

[1] Moyer HR, Delman KA: The role of hyperthermia in optimizing tumor response to regional therapy. Int J Hyperthermia. 24, 251-61 (2008)
[2] Sahinbas H, Groenemeyer DHW, Boecher E, Szasz A. Retrospective clinical study of adjuvant electro-

hyperthermia treatment for advanced brain-gliomas. Deutche Zeitschrifts fuer Onkologie, 39, 154-160 (2006)
[3] Singh BB: Hyperthermia - a new dimension in cancer treatment. Indian J Biochem Biophys. 27(4), 195-201 (1990)
[4] Szasz A: Physical background and technical realization of hyperthermia, In: Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects. Baronzio GF, Hager ED (Eds.) Springer Science Eurekah.com, Ch.3., 27-59 (2006)
[5] Roemer RB: Engineering aspects of hyperthermia therapy. Ann Rev Biomed Eng. 1, 347–76 (1999)
[6] Hegyi G, Szigeti GP, Szasz O, Szasz A: Hyperthermia versus Oncothermia: Cellular effects in cancer therapy. Accepted for publication. Evidence-Based Complementary and Alternative Medicine. http://www hindawi.com/journals/ecam/aip/672873/
[7] Coffey DS, Getzenberg RH, DeWeese TL: Hyperthermic biology and cancer therapies: a hypothesis for the "Lance Armstrong effect". JAMA. 296(4), 445-8 (2006)
[8] Joseph L. Roti Roti: Cellular responses to hyperthermia (40–46C): Cell killing and molecular events Int. J. Hyperthermia 24, 3–15 (2008)
[9] Kampinga HH, Dynlacht JR, Dikoney E: Mechanism of radiosensitzation by hyperthermia (43oC) as derived from studies with DNA repair defective mutant cell lines. International Journal of Hyperthermia 20, 131–139 (2004)
[10] Laszlo A. The effects of hyperthermia on mammalian cell structure and function. Cellular Proliferation 25, 59–87 (1992)
[11] Coss RA, Dewey WC, Bamburg JR: Effects of hyperthermia on dividing Chinese hamster ovary cells and on microtubules in vitro. Cancer Res 42, 1059–71 (1982)
[12] Kregel KC: Heat shock proteins: modifying factors in physiological stress responses and acquired thermotolerance. Journal of Applied Physiology 92, 2177–2186 (2002)
[13] Westra A, Dewey WC: Variation in sensitivity to heat shock during the cell-cycle of Chinese hamster cells in vitro. Int J Radiat Biol Relat Stud Phys Chem Med 19, 467–77 (1971)
[14] Iwata K, Shakil A, Hur WJ, Makepeace CM, Griffin RJ, Song C: Tumour pO2 can be increased markedly by mild hyperthermia. Br J Cancer 74(suppl. XXVII), S217–S221 (1996)
[15] Vidair C, Dewey WC: Two distinct modes of hyperthermic death. Radiat Res 116, 157–71 (1988)
[16] Gyldenhof B, Horsman MR, Overgaard J: Hyperthermia-induced changes in the vascularity and histopathology of a murine tumour and its surrounding normal tissue. In: Franconi C, Arcangeli G, Cavaliere R, editors. Hyperthermic oncology. Vol. II. Rome: Tor Vergata; 780–782 (1996)
[17] Vaupel P, Kallinowski F, Okunieff P: Blood flow, oxygen and nutrient supply, and metabolic micro-environment of human tumors: A review. Cancer Res 49, 6449–6465 (1989)
[18] Vaupel PW: Effects of physiological parameters on tissue response to hyperthermia: New experimental facts and their relevance to clinical problems. In: Gerner EW, Cetas TC, editors. Hyperthermia Oncology 1992. Tucson: Tucson Arizona Board of Regents 17–23 (1993)
[19] Vaupel PW, Kelleher DK: Pathophysiological and vascular characteristics of tumours and their importance for hyperthermia: heterogeneity is the key issue. Int J Hyperthermia 26, 211-23 (2010)
[20] Szentgyorgyi A (1998) Electronic Biology and Cancer. Marcel Dekkerm New York
[21] Vaupel P, Kelleher DK: Metabolic status and reaction to heat of normal and tumor tissue. In: Seegenschmiedt MH, Fessenden P, Vernon CC, editors. Thermoradiotherapy and Thermochemotherapy. Vol. 1. Berlin, Heidelberg, New York: Springer; 157–176 (1995)
[22] Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, Felix R, Riess H: The cellular and molecular basis of hyperthermia. Crit Rev Oncol Hematol. 43, 33-56 (2002)
[23] Kai H, Suico MA, Morino S, Kondo T, Oba M, Noguchi M, Shuto T, Araki E: A novel combination of mild electrical stimulation and hyperthermia: general concepts and applications. Int J Hyperthermia. 25, 655-60 (2009)
[24] Lindquist, S: The heat-shock response. Ann. Rev. Biochem. 55, 1151-1191 (1986)
[25] Torigoe T, Tamura Y, Sato N: Heat shock proteins and immunity: application of hyperthermia for immunomodulation. Int J Hyperthermia. 25, 610-6 (2009)
[26] Andocs G et al. Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model. Radiology and Oncology (Strahlentherapie und Onkologie) 185, 120-126 (2009)
[27] Andocs G, Renner H, Balogh L, Fonyad L, Jakab Cs, Szasz A. Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model, Radiology and Oncology [Strahlentherapie und Onkologie], 185, 120-126 (2009)
[28] Andocs G, Szasz O, Szasz A. Oncothermia treatment of cancer: from the laboratory to clinic. Electromagnetic in Biology and Medicine. 28(2), 148-165 (2009)
[29] Gijn van ME, Snel F, Cleutjens JPM, Smits JFM, Blankesteijn WM. Overexpression of Components of the Frizzled-Dishevelled Cascade Results in Apoptotic Cell Death, Mediated by b-Catenin. Experimental Cell Research 265, 46–53 (2001)

Oncothermia Journal 7:343-347 (2013)

Bystander effect of oncothermia

Andocs G[1], Meggyeshazi N[2], Okamoto Y[1], Balogh L[3], Szasz A[4]

(4) Department of Veterinary Clinical Medicine, School of Veterinary Medicine, Tottori University, Tottori, 4-101 Minami, Koyama-cho., tottori Pref., Japan

(5) 1sr Department of Pathology and Experimental Cancer Research, Semmelweis University, 1085-Budapest, Ulloi ut 26., Hungary

(6) "Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene 1221-Budapest, Anna u. 5., Hungary

(7) Department of Biotechnics, Szent Istvan University, 2100-Godollo, Pater K. u. 1., Hungary

Corresponding author: Gabor Andocs gandocs@gmail.com

This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

Bystander effect of oncothermia

Background

Oncothermia (OTM) is an electro-hyperthermia modality, a long time (since 1989) applied method, [1], used successfully in human oncology [2]. OTM changes the paradigm of hyperthermia by targeted microscopic heat-liberation at the membrane of the malignant cells. This method creates inhomogeneous heating, and the microscopic temperature greatly differs far from the thermal equilibrium. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier by a laboratory research, and were presented elsewhere [3], [4]. Bystander effect (abscopal effect) means that a local tumor treatment can affect the behavior of the far distant metastases. It was first discovered by radio-oncologists and remained a highly controversial topic until recent years. [5], [6]. Intensive research is being conducted to reveal the immunbiological basis [7], [8], [9] and the mechanism of the action of this effect [10] and to use the benefits in the regular oncological practice. Our objective is to show the newest results of oncothermia in research of the bystander effect.

Materials and methods

Animal model

HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mice. The use of the mice and the procedures used in this study were approved by the Animal Experiment Ethical Committee of National Research Institute for Radiobiology and Radiohygiene.

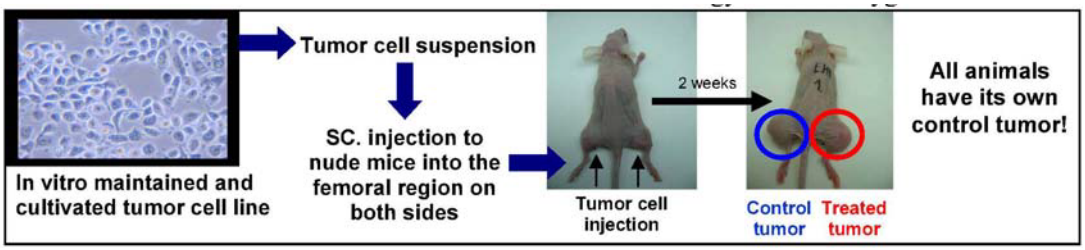


Figure 1. Process of the tumor induction of the experimental animals

Experimental setup and treatment

A single shot 30 min oncothermia treatment was done, reaching maximum 41-42oC intratumoral temperature, using the LabEHY system (Oncotherm Ltd. Germany), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense, Luxtron m3300).

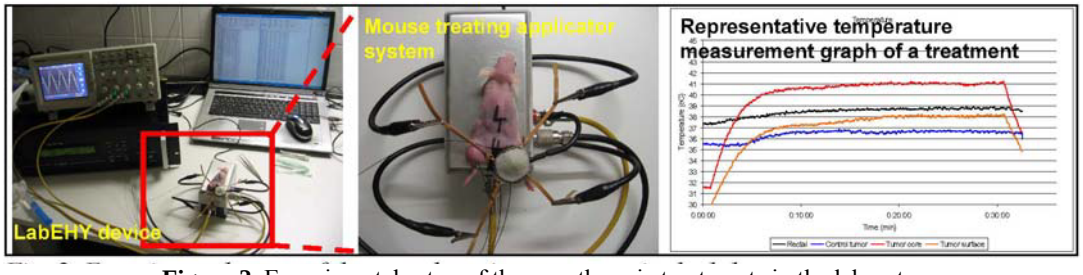


Figure 2. Experimental setup of the oncothermia treatments in the laboratory

Study design: Time course study was performed. After a single shot treatment, sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 hours. 3 mice were sacrificed at each time point, keeping 5 sham treated animals.

Figure 3. All the oncothermia-treated experimental animals involved in this study

Tumor sample processing: At the time of the sampling the single-treatment animals were sacrificed and both the control and treated tumors were removed and studied in pairs.

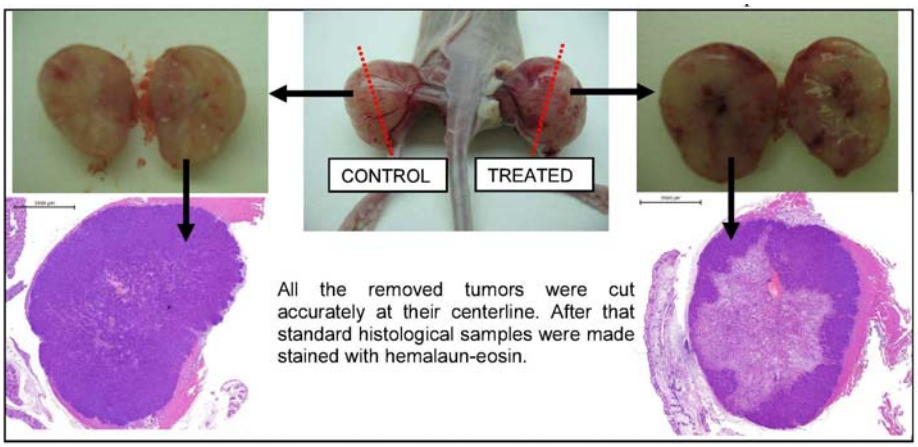


Figure 4. Method of the tumor sample processing

Due to the extremely high number of the tumor samples, tissue microarray (TMA) technology was used to perform accurate immuno-histochemical reactions on many samples in one block.

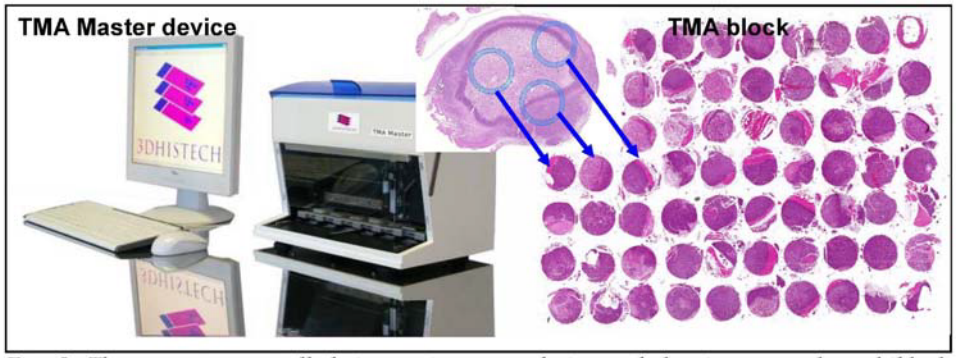


Figure 5. The computer-controlled tissue-microarray device and the tissue sample multiblock were created by the TMA Master device (3DhisTech). One multiblock contains many small representative tumor tissue samples, so really identical and highly standardized immunohistochemical reaction can be performed in all the samples. This is the real advantage of this technology

Immunohistochemistry (IHCH): The following reactions and IHCH analysis were performed on the TMA samples: TUNEL (Invitrogen); TRAIL-R2 (DR5) (Cell Signaling), HSP70 (Cell Signaling); Myeloperoxidase (Sigma); CD3 (Dako), CD4 (ABDSerotech).

Digital microscopy analysis: All histological slides were digitalized using Panoramic Slide Scanner (3D HisTech) and a special software was used for imaging and evaluation.

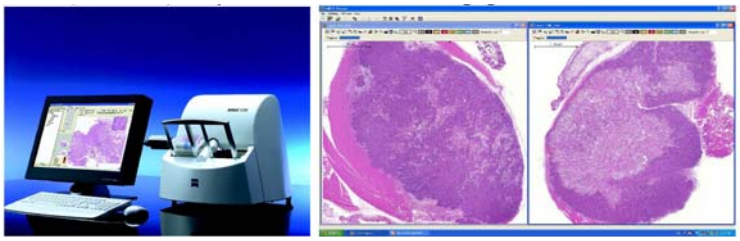


Figure 6. The panoramic slide scanner device and a screenshot from the panoramic viewer software, dedicated for prectise histomorphological analysis

Results

1. Histomorphological changes

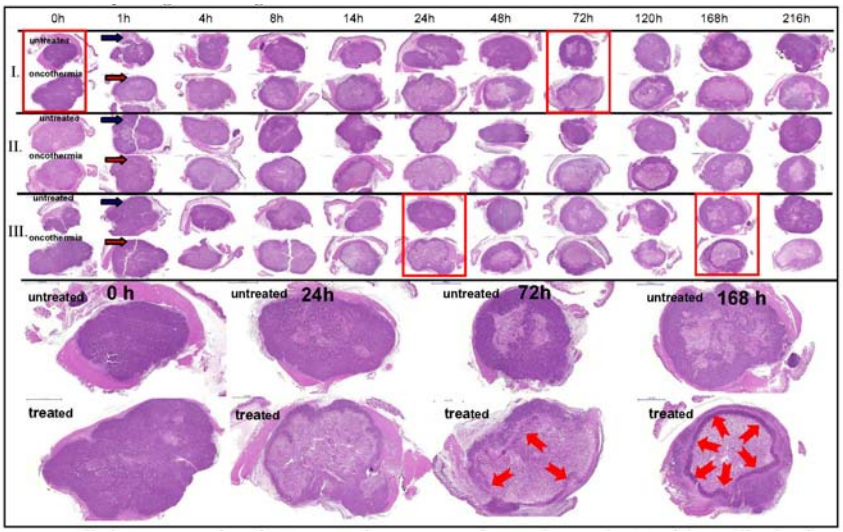


Figure 7. All the processed and HE stained tumor samples in this study. Morphologically the first significant sign of cell destruction was seen 8H after the treatment. Drastic and selective tumordestruction was detected 24H after OTM which became more emphasized after 48H. 72 hours after the treatment a significant leucocyte infiltration (marked with red arrows) appeared around the destructed tumor tissue and reached its maximum 168 hours after the treatment

2. Appearance of the hallmarks of immunogenic cancer cell death

2.1. Apoptotic body formation

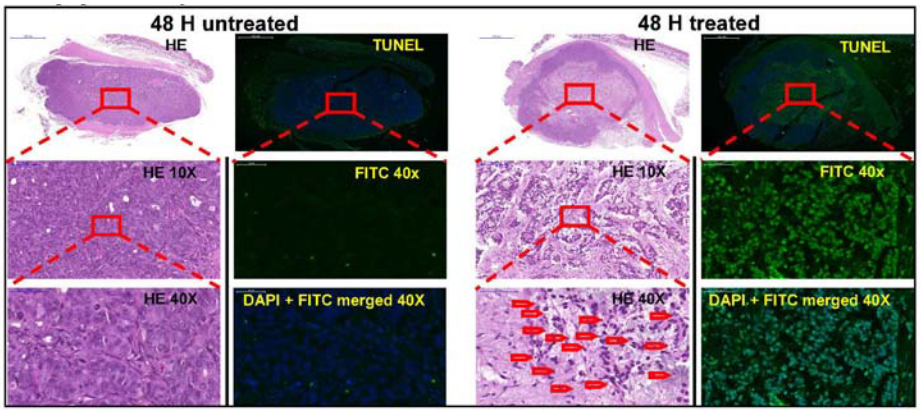


Figure 8. HE and TUNEL stained whole cross-section tumor samples 48H after the treatment. Oncothermia treatment induce apoptotic cell death, and this process is highly emphasized 48H after a single shot treatment. Almost all the cell nuclei of the killed tumor cells are TUNEL positive. In the process of this programmed cell death a huge number of apoptotic bodies were formed (marked with red arrows)

2.2. TRAIL-R2 (DR5) expression

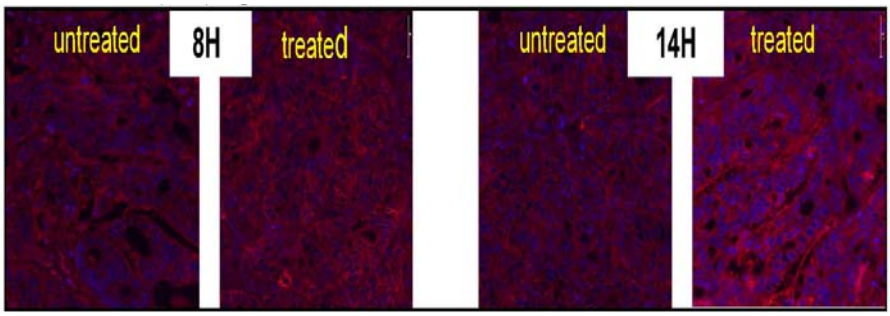


Figure 9. TRAIL-R2 detection IHCH from TMA multiblock TRAIL-R2 (DR5) is a highly immunogenic cell surface receptor. Expression was increased in the treated side 8H after the treatment and became more emphasized after 14H

2.3. HSP70 expression changes and molecular dynamics

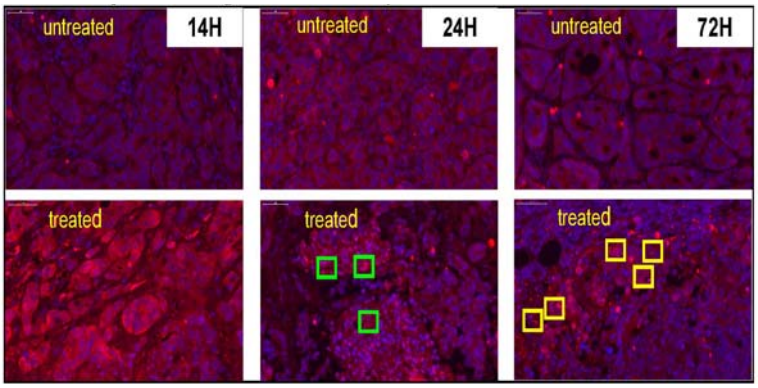


Figure 10. HSP70 detection IHCH from TMA multiblock. Definite increase of the HSP70 expression was observed 14 hours after the treatment. After 24 hours, unusual molecular dynamic changes of the increased amount of HSP70 can be visible: intracellular condensation (marked with green rectangle) and relocalization to cell membrane. After 72 hours the membrane relocalization of the HSP70 became more emphasized, especially in the region of the leukocyte invasion (marked with yellow rectangle)

3. Strong local immune reaction

3.1. Mycloperoxidase (MPO) detection

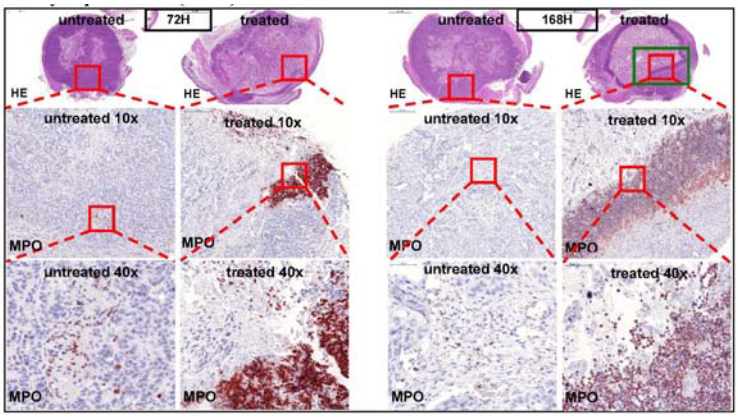


Figure 11. Myeloperoxidase (MPO) detection from TMA multiblock. MPO is a marker of neutrophyle granulocytes. The leukocyte invasion ring which appears at 72H and becomes very characteristic at 168H around the destructed tumor area, contains high number of MPO positive cells (neutrophils)

3.2. CD3, CD4 detection

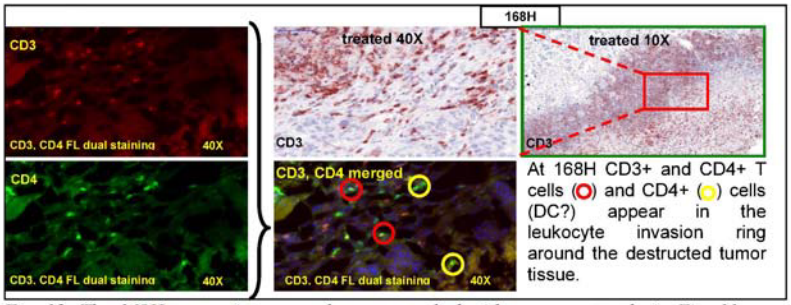


Figure 12. The 168H tumor tissue sample area, marked with green rectangle in Fig. 11. Was analyzed by CD3 IHCH staining and , CD3/CD4 dual fluorescent IHCH staining. The analysis showed that the invasion ring, beside the neutrophiles, also contains large amount of CD3+ T cells and CD4+ cells, probably dendritic cells

Conclusions

1. Oncothermia treatment can induce programmed cell death in the tumors which create many apoptotic bodies. Presence of apoptotic bodies in a destructed tumor tissue is essential to induce immunogenic reactions.
2. Oncothermia treatment induced cell death is highly immunogenic, showing all the key molecular pattern dynamic changes what is characteristic of immunogenic tumor cell death.
3. Oncothermia treatment can induce strong and very unusual local immune reaction at the site of the treatment, long time after the electromagnetic intervention.
4. The local antitumor immune reaction of oncothermia treatment might be systemic, if the host has an intact immune system, and a proper immune-stimulating agent is administered. This process can control the distant metastases by bystander effect, making the systemic control of the malignant disease possible with local treatment. Ongoing intensive research is in progress on immunocompetent tumor models, to investigate and reveal the mechanisms of the action of this controlled bystander effect.

References

[1] Szasz A. (2007) Hyperthermia, a modality in the wings, J Cancer Res Ther. 3:56-66.
[2] Szasz A. Szasz N. Szasz O. (2010) Oncothermia. Principles and Practices, Springer Verlag, Heidelberg, Dordrecht
[3] Andocs G, Szasz O, Szasz A. (2009); Oncothermia treatment of cancer: from the laboratory to clinic, Electromagn Biol Med. 28(2):148-65.
[4] Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Strahlenther. Onkol. Feb;185(2):120-6.
[5] SC Formenti, S Demaria : Systemic effects of local radiotherapy, Lancet Oncol 2009: 10:718–26
[6] WF. Morgan, MB. Sowa, Non-targeted bystander effects induced by ionizing radiation, Mutation Research 616 (2007) 159–164
[7] RPA.Wallin, A Lundqvist, SH. Moré, A von Bonin, R Kiessling,H-G Ljunggren, Heat-shock proteins as activators of the innate immune system, TRENDS in Immunology Vol.23 No.3 March 2002
[8] SR. Scheffer, H Nave, F Korangy, K Schlote, R Pabst, EM. JAFFEE, Apototic but not necrotic tumor cell vaccines induce a potent immune response in vivo, Int. J. Cancer: 103, 205–211 (2003)
[9] O Kepp, A Tesniere, F Schlemmer, M Michaud, L Senovilla, L Zitvogel, G Kroemer. Immunogenic cell death modalities and their impact on cancer treatment, Apoptosis (2009) 14:364–375
[10] AD. Garg, D Nowis, J Golab, P Vandenabeele, DV. Krysko, P Agostinis, Immunogenic cell death, DAMPs and anticancer therapeutics: An emerging amalgamation, Biochimica et Biophysica Acta 1805 (2010) 53–71

Oncothermia Journal 7:349-356 (2013)

Oncothermia with chemotherapy in the patients with small cell lung cancer

Doo Yun Lee[1], Seok Jin Haam[1], Tae Hoon Kim[2], Jae Yoon Ihm[3], Eun Jung Kim[1], Na Young Kim[1]

(1) Department of Thoracic & Cardio-vascular Surgery, Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea

(2) Department of Diagnosti Radiology, Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea

(3) Department of Medical Oncology, Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul, Korea

This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

Oncothermia with chemotherapy in the patients with small cell lung cancer

Abstract

Small cell lung cancer constitutes approximately 13% of all lung cancer types & SCLC is one of the most aggressive and lethal forms of lung cancer. And so chemotherapy including radiotherapy would be standard for SCLC, but it has very poor median survival of less than 4 months. This is why another form of additional treatment to chemotherapy would be necessary and so oncothermia will be one of the additive treatment for prolonged survival time.

We made a 6 year-long study of 31 patients with small cell lung cancer at the department of Thoracic & Cardiovascular surgery Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul from April 2006 to March 2012.

23 patients were treated with chemotherapy and oncothermia and 8 patients were treated with chemotherapy only.

1. Cases who have survived more than 3 years were 3. They have been treated with chemotherapy and oncothermia
2. Out of 31 cases, 14 patients died during the treatment, 7 cases with chemotherapy only died, including one long survival case of 28 months, 7 cases with chemotherapy and oncothermia died, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are still alive: 4cases were treated with chemotherapy only, including one long survival case of 28.7 months, 11cases with chemotherapy and oncothermia including three long survival cases of more than 3 years
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value 0.0200). Combination of oncothermia treatment with chemotherapy enhance the effect of anticancer drugs to destroy cancer cells and is thought to be able to improve the survival of the patients with small cell lung cancer.

Introduction, background

Lung cancer is one of the most common causes of cancer-related deaths in both men and women worldwide. Its incidence as well as the mortality rates are high, and the prognosis is usually very poor, [1]. In 2006 its age-standardized incidence and mortality rates were estimated to be 75.3 and 64.8/100 000/year, respectively, in men, and 18.3 and 15.1/100 000/year in women in Europe, where the small-cell lung cancer (SCLC) accounts for 15%–18% of all cases [2].The small-cell lung cancer has a fast growth-rate, it quickly disseminates quickly around the mediastinal lymph nodes and forms distant metastases in late diagnosis, and then the median survival is only 2-4 months, the overall prognosis is very poor, [3], [4].

In almost all small-cell lung cancer cases, surgical treatment is not possible it could only be performed only in very limited disease (i.e. T1,N0) [2]; consequently, the main treatments are the chemo- and radiation therapy. In general case of SCLC, even if some reported long-term survival, the overall 2-year survival rate is less than 20%. 5-year survival rate is almost devoid. In limited SCLC, chemotherapy alone reached complete remission (CR) in 50% of relapse cases. Bulky primary tumors were completely destroyed but most of intrathoracic recurrence was difficult to discover. Added to radiation therapy [5] In this case, 30 - 60% recurrence rate has been reduced, radiation pneumonitis, esophagitis, and the overall survival rate was significantly improved. [6]. In addition, initially most of the extensive small-cell lung cancer with advanced small-cell lung cancer, chemotherapy response joteuna for anticancer drug resistance may occur and the overall survival rate was very poor, median survival was 7-10 months ,2-year survival rates of the less

Lung cancer is one of the most common cause of cancer-related deaths in both men and women worldwide. Its incidence as well as mortality rates are high, and the prognosis is usually very poor, [1]. Its age-standardized incidence and mortality rates in 2006 were estimated to be 75.3 and 64.8/100 000/year, respectively, in men, and 18.3 and 15.1/100 000/year in women in Europe, where the small-cell lung cancer (SCLC) accounts for 15%–18% of all cases [2].The small-cell lung cancer has a fast growth-rate, disseminated quickly around the mediastinal lymph nodes and forms distant metastases in late diagnosis, and then the median survival is only 2-4 months, the overall prognosis is very poor, [3], [4].

In almost all small-cell lung cancer cases, surgical treatment is not possible it could be performed only in very limited disease (i.e. T1, N0) [2]; consequently the main treatments are chemo- and radiation therapy. In general case of SCLC, even if some reported long-term survival, the overall 2-year survival rate is less than 20%. 5-year survival rate is almost devoid. In limited SCLC, chemotherapy alone reached complete remission (CR) in 50% of relapse cases. Bulky primary tumors completely were destroyed but most of intrathoracic recurrence was difficult to discover. Added to radiation therapy [5] In this case, 30 - 60% recurrence rate has been reduced, radiation pneumonitis, esophagitis, and the overall survival rate was significantly improved. [6]. In addition, initially most of the extensive small-cell lung cancer with advanced small-cell lung cancer, chemotherapy response joteuna for anticancer drug resistance may occur and the overall survival rate was very poor, median survival was 7-10 months ,2-year survival rates of the less than 5%, the prognosis was poor. According to a report from the University of Toronto 119 SCLC, median survival 111 weeks and 5-year survival rate was 39% and stage-specific survival in 51%, based on the 28% for stage and based on the 19% for stage prognosis was poor. [7].

The most widely used chemotherapy is the Etoposide/Cisplatin (EP) treatment which has a median survival of 8-10 months for patients with extensive disease and 17-20 months for patients with limited-disease, [8].

The concurrent radiotherapy with chemotherapy is used as an optimal treatment for limited SCLC, [9].

Chemotherapy and radiation therapy were performed on the tumor after complete resection and the relationship did not cause death in 19 patients with autopsy and in 13 patients with small-cell lung cancer metastases have been cured [10]. The prognosis of SCLC is generally poor, because micro-metastases occur and surgical resection is not possible. There are frequently occurring insidious transitions [10], [11].

In a study of chemo- and radiation therapies [12] for 28 patients died of other causes than lung cancer has been reported, and 47% was clinically cured. The autopsy study [13] of patients who died from other causes than tumors found that residual cancer cells in the area of lung cancer and mediastinal lymph node regions are 64%.

The prognostic index was constructed for SCLC in Severance hospital, (Korea), retrospectively evaluation of 295 patients revealed 131 cases with limited and 164 cases with extended disease. The median survival was 20.4 months for limited and 7.7 months for extended disease, [14]. A prognostic index was constructed to create four classifications of SCLC considering the variables of the extension of the disease, the performance status, the CYFRA21-1 and the tumor-marker.

Heat therapy could be a feasible option to treat SCLC. The classical loco-regional heat treatment (conventional oncological hyperthermia) has a localized area selection [15]. This boosts the chemo-efficacy, [16], [17], [18] and also increases the effectiveness of radiation therapy [19], [20].

Some successful clinical trials had shown the feasibility of the hyperthermia method for lung cancer. Most of these are applied for non-small-cell lung cancer (NSCLC), combined with radiotherapy, having 14÷70 Gy dose in the given session. The measured response rate (RR) was surprisingly high RR=75%, (n=12, [21]), and RR=100% (n=13, [22]). Others had a comparison to a control-arm (not randomized), increasing the RR from RR=70% (n=30), and RR=53.8% (n=13), to RR=94.7% (n=19, [23]), and RR=76.9% (n=13, [24]), respectively. The second year survival also increased remarkably: from 15% and 15.4% to 35% and 44.4%, respectively. (The first year survival was measured as well, increasing from 30% to 55%, [23]).

The chemo-thermotherapy combination was also investigated for NSCLC with success. In preclinical trials the cisplatine was shown to be effective, [25], so the clinical studies were concentrating on this drug combination. A special case report showed the feasibility [26], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [27]. The median survival was measured in another study [28], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5year median survival was measured in another study [29], showing rather high numbers (24.5%, n=30).

However, a problem arises by the classical hyperthermia. The cancer tissue is more active than the surrounding normal tissue, its cell proliferation and metabolism require a lot of energy. When temperature tries to equalize itself in the surrounding, it grows around the tumor. In consequence the surrounding blood vessels expand, the blood flow increases delivers extra nutrition for tumor accelerating its stable proliferation. In this case, the temperature rise of the cancerous tissue will have more metabolic and proliferation activity. Furthermore, hyperthermia effects the intracellular Heat-Shock Proteins (HSP), developing thermo-tolerance of the cells, [30].

The extracellular matrix surrounding the tumor is overburden by ionic metabolites and final metabolic products, which changes their electric properties [31]. [32]. This is used by oncothermia when selecting

the tumorous region, and at the same time absorbing the energy selectively on the malignant cells. The temperature rises only very locally on the malignant cells, and does not rise all over the large volume and does not affect the surrounding normal tissue. In consequence no vasodilatation occurs, no extra proliferation is supported by the blood vessels, the absorbed energy concentrates on the job: destroy only the tumor [33].The method works by impedance tuned, capacitive coupled radiofrequency, with modulated 13.56 MHz.

One of the most advanced hyperthermia-modalities devoted to oncology is oncothermia [33]. The actions widely affect the targeted malignant cells: passing through the malignant cell membrane 1500 nW/μm2 heat-flow, while the normal tissue membranes have only 20 nW/μm2 Oncothermia treatment induces Na+ influx current 150 pA/μm2 while normal Na+ efflux is 12 pA/μm2, [34]. Na+ moves into the malignant cell, the water is also pumped in by electro-osmotic way, increasing the pressure within the cell. By these actions the cell membrane is destroyed and will destroy the cancerous tissue. [35]. For these reasons we expect the effect on the disseminated SCLC lesions with the combination of chemotherapy and radiation therapy. We supposed improved survival rates, when appropriate amount of energy, proper temperature, well-chosen doses, are used in the study [33].

In the preliminary reports [36], [37], [38] the feasibility of oncothermia application was demonstrated on NSCLC and some preliminary case reports and statistical summaries on SCLC were presented in local conferences too, [39], [40]. Systematic study of oncothermia applications for SCLC is still missing. Our present study tries to provide more details in this important field of oncology.

Materials and methods

A prospective, double arm, monocentric study for SCLC was performed. The small-cell lung cancer cases were treated with a combination of chemotherapy and radiation therapy, with complementary oncothermia in our study. It is considered that the applied complex protocol completed by oncothermia maximizes the effectiveness of chemotherapy and may improve the survival rate. We treated 31 patients in duration of 6 years, from April 2006 to March 2012.

7 out of 8 cases in control arm who underwent only chemotherapy were men, and in one case was a woman. The youngest was 54 years old and the oldest was 84 years old. The active arm, 23 patients had the combination of chemotherapy and oncothermia treatment, 19 males and four females. The youngest was 54 years old, the oldest was 79 years old (see table 1.). There was no significant difference between these two groups (Fisher's exact test:> 0.9999; t-test: p-value => 0.8665). The real end-point of the study was the survival time.

All patients had proven SCLC and received chemotherapy. 23 patient received oncothermia in combination with chemotherapy. Oncothermia was provided with EHY-2000 device (Oncotherm GmbH, Germany).

Anticancer drugs in the first-line were Irinotecan (60 mg/ m²) and Cisplatin (60 mg / m²) three times after the chest CT was taken. When the progression of tumor or metastases was detected we replaced the chemotherapy regime by Etoposide (110 mg / m²) and Cisplatin (70 mg / m²) in the second line.

Oncothermia was performed from the first anti-cancer drug treatment period up to 150Watt, 1,490.5 kJ energy by 60 minutes, every second day, with rise in temperature from 38.5°C-42.5°C. In this study we used a 30 cm diameter electrode applied for thorax. Other technical details are shown elsewhere [33], [41].

	CTX.* only			CTX. + Oncothermia			
Age	M	F	Total	M	F	Total	Total
51 – 60	2	-	2	5	1	6	8
61 - 70	4	-	4	8	2	10	14
71 - 80	1	-	1	6	1	7	8
81 - 90	-	1	1	-	-	-	1
	7	1	8	19	4	23	31

Table 1. Patient's profile

Characteristic cases

A male patient aged 67 who had visited our Department with chief complaints of slight fever and sputum in August 2008 was hospitalized for a thorough examination and then diagnosed as a case of limited small cell lung cancer. For treatment, Irinotecan (60mg/m²) and Cisplatin (60mg/m²) were administered 12 times and at the same time, oncothermia was given 24 times (2 cycles) in total, 2 times per week. Then, chest PA and chest CT revealed that he was in complete remission from small cell lung cancer. So, treatments of chemotherapy and oncothermia were stopped from October 2009 and then he was an outpatient follow-up on a regular basis. On Oct. 25th 2010 PET CT showed a normal finding. In April 2011 he was treated by chemotherapy in the Department of Urology, our hospital, for prostatomegaly. Because of the fact that PSA was increased to 4.96 in June 2011, he got a prostate tissue biopsy and was diagnosed with a case of adenocarcinoma. Finally he was treated with the prostate cancer resection using the Da Vinci robot in July 2011. Chest CT was done in July 2011, it found mediastinal lymphadenopathy, and after mediastinoscopy, he was diagnosed as a case of metastatic small cell lung cancer. For chemotherapy, Etoposide (110mg/m²) and Cisplatin (70mg/m²) were 12 times administered in replacement, and another one-cycle treatment of oncothermia was given. In Dec. 2011 and Feb. and April 2012, follow up chest CT found that the patient was in complete remission. During outpatient follow-ups in Sept. 2012, chest CT found multiple nodes in the left upper and lower lobes on possible suspicion of metastasis. Under the patient's personal circumstances including general weakness, chemotherapy and oncothermia were stopped, and he had been now observed in outpatient follow-up for more than 3 years. [6]

Three month later, the check up showed good partial remission (PR) on the lesion, (figure 1.), patient is free from symptoms.

Our case to present is a 67-year-old male, registered with symptoms of cough, low-grade fever in August 2009. The diagnosis was SCLC, (see Figure 1.).

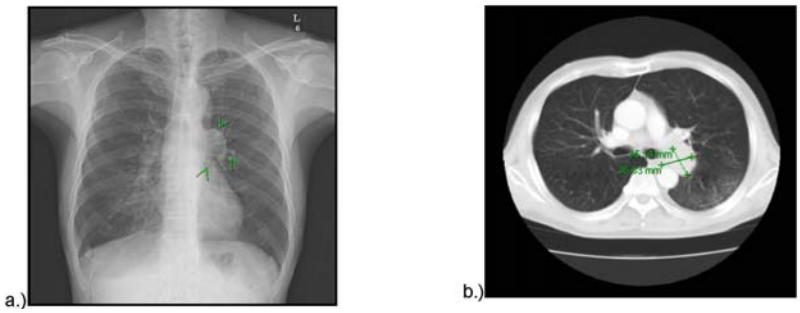


Figure 1. (a) Chest X-ray: in the left hilar lung tumors are found . (b) Chest CT: Left hilar lung tumor approved [21. Jul. 2009]

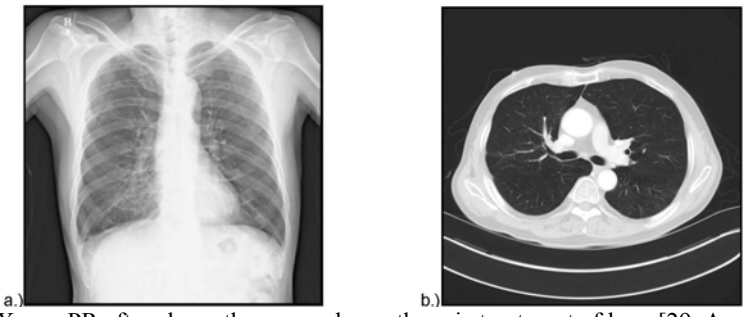


Figure 2. (a) Chest X-ray: PR after chemotherapy and oncothermia treatment of lung [29. Apr. 2010], (b) Chest CT: approved the PR [30th. Apr. 2010]

Nine month later PR was observed, (see Figure 2.), patient is free from symptoms.

Another case to present is a male patient 65 years old, registered in January 2010, diagnosed by SCLC, (see Figure 3.).

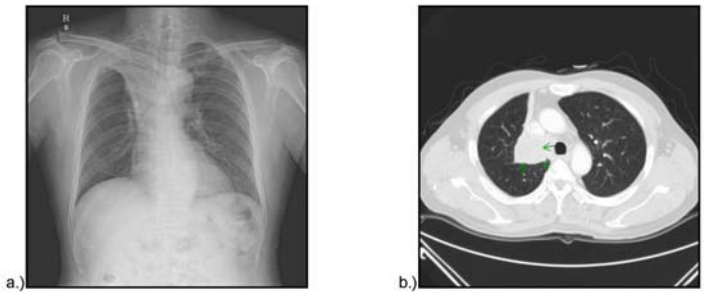


Figure 3. (a) Chest X-ray:: the right upper lobe bronchus obstruction due to cancer as atelectasis is observed, [6th. Jan. 2010]. (b) Chest CT: right upper lobe bronchus and bronchial cancer is proven in the right upper lobe atelectasis, [7th. Jan. 2010]

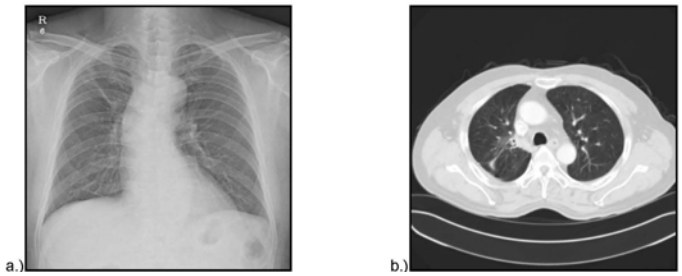


Figure 4. (a) Chest X-ray: after chemotherapy and oncothermia treatment of the right upper lobe atelectasis was not observable. (b) Chest CT: right upper lobe bronchus, bronchial cancer was disappeared [23. Nov. 2010]

Eleven months later we reached complete remission (CR), (see Figure 4.).
He is follow-up on OPD to now more than 1year after chemotherapy and oncothermia was stopped with good general condition for more than 3 years.

Study results

Chemotherapy alone (without oncothermia) was applied for eight cases. The survival time ranged from 2 months up to 29 months. With the combination of chemotherapy and oncothermia, the survival time was from 2 months to up to 36 months.
The treatment was terminated for only 1 patient. It was within 1 month after the diagnosis and treatment with chemotherapy only. All other 31 patients underwent chemotherapy and 23 had combined treatment with oncothermia.
1. Among 23 cases, one paient died within one month after the date of diagnosis, who was treated with chemotherapy only. Cases who have survived more than 3 years were 3, all of whom were treated with the combined use of chemotherapy and oncothermia.
2. Out of 31 cases, 14 died during the treatment; (i) 7 were treated with chemotherapy only, including one long survival case of 28 months, and (ii) 7 ones treated by the combined use of chemotherapy and oncothermia, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are alive up to the present: 4 got chemotherapy only, including one long survival case of 28.7 months, and (ii) 11 were treated by the combined use of chemotherapy and oncothermia, including three long survival cases of more than 3 years.
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value = 0.0200)

The survival analysis shown by the Kaplan-Meier curve survival distribution (see Figure 5.) shows significant difference between the arms of chemotherapy with and without oncothermia. The log-rank test to compare survival distributions between the two groups, had hazard ratio and 95% confidence interval using Cox proportional hazard regression shown p=0.02. The summary is shown in Table 2.

Summary of the Number of Censored and Uncensored Values					
Stratum	Group1	Total	Failed	Censored	Percent Censored
1	chemotherapy	8	7	1	12.50
2	oncothermia in parallel	23	12	11	47.83
Total		31	19	12	38.71

Table 2. Comparison of the arms with chemotherapy without and with oncothermia in parallel

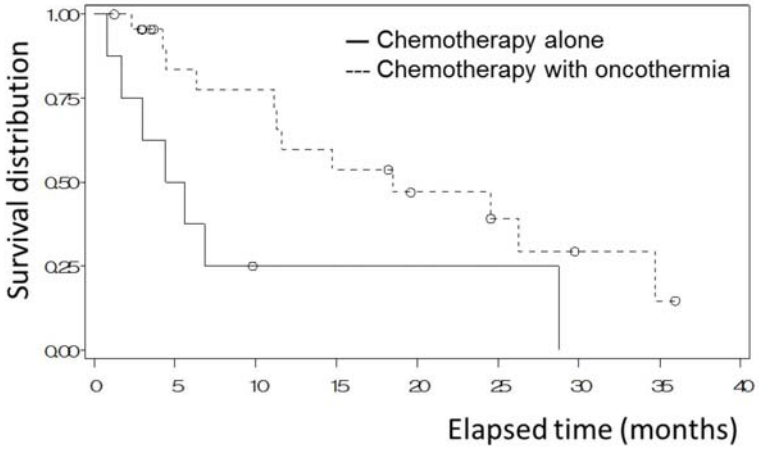


Figure 5. Kaplan-Meier survival curve. ⇒log-rank test, p-value=0.0200

Conclusion

1. In the cases of small cell lung cancer, we obtained a better treatment efficacy than with the treatment of chemotherapy only, by the combined use of chemotherapy and oncothermia (one hour per each time, 2 times per week, and more than 12 times (= one cycle)). Based on this, our thought is that the treatment of oncothermia, 3 times per week and more than 3 cycles, can create a good treatment efficacy
2. Small cell lung cancer can primarily be covered by chemotherapy (and radiotherapy sometimes), but tolerance against the anti-cancer agent is frequently created and then the return of the disease or metastasis takes place very often, which indicates a poor prognosis. We think that the combined use of oncothermia can enhance the treatment efficacy of chemotherapy, thus getting a higher rate of survival against small cell lung cancer.
3. However, we have some limitations of not so many cases with chemotherapy and oncothermia and short periods of follow-up. We consider that more cases and longer periods of follow-up are required for a good verification.
4. Several matters including the most suitable size of energy, time of administration and the number of administrations should be the subjects of subsequent studies.
5. Combination of oncothermia treatment applied to enhance the effect of anticancer drugs to destroy cancer cells is thought to be able to improve the survival of small-cell lung cancer. However, the author of chemotherapy and hyperthermia our case, less than the observation period is shorter than many cases and long-term follow-up will be necessary.

The hyperthermia dose, that is the amount of energy, and the appropriate time of administration, the number of doses, should be further studied.

Chemotherapy in SCLC, the authors and twice a week, one hour of treatment, more than 12 times (1 cycle), treatment with a combination of hyperthermia treatment effects compared to chemotherapy underwent example was good. It three times a week, 3 cycles or hyperthermia treatment effect is good thought.

In case of small cell lung cancer recurrence or metastasis, chemotherapy, and in some cases, radiation therapy may be added frequently, the anti-cancer drug for the treatment of resistant wounds, the prognosis is poor.

References

[1] Owonikoko TK, Ragin CC, Belani CP, et al. Lung cancer in elderly patients: an analysis of the surveillance, epidemiology, and end results database. J Clin Oncol. 2007;25:5570-5577

[2] M. Sørensen1, M. Pijls-Johannesma2 & E. Felip; On behalf of the ESMO Guidelines Working Group; Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up; Annals of Oncology 21 (Supplement 5): v120–v125, 2010

[3] Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, et al. Timing chest radiotherapy in patients with limited stage small cell lung cancer a systematic review and meta-analysis of randomised controlled trial.

Cancer Treat Rev. 2007;33:461-473
[4] Samson DJ, Seidenfeld J, Simon GR, et al. Evidence for management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 2007;132(3 Suppl):314S-23S
[5] William CJ, McMillan I, Lea R, Mead G, Thompson J, Sweetenham J, Herbert A, Jefferys M, Buchanan R, Whitehouse JM: Surgery after initial Chemotherapy for localized Small-cell carcinoma of the lung. J Clini Oncol 1987;5:1579
[6] Turrisi AT III, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340:265-271
[7] Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E. Surgical treatment for limited small-cell lung cancer. The University of Toronto Lung Oncology Group experience. J Thorac Cardiovasc Surg 1991;101(3):385-393
[8] J. S. Lee, J. Han, S. Yu, S. Yoon, E. Lim, H. Pyo, H. Kim, D. Lee, H. Kim, K. Cho, G. Lee; The progress of small cell lung cancer management using irinotecan plus cisplatin chemotherapy; Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 7721
[9] Keunchil Park, Jong-Mu Sun, Sang-We Kim, Myung-ju Ahn, Jin Seok Ahn, Dae Ho, Lee, Cheolwon Suh, Yong Chan Ahn, Hongryull Pyo, Eun Kyung Choi, Si Yeol, Song, Se-Hoon Lee; Jung Shin Lee; Phase III trial of concurrent thoracic radiotherapy (TRT) with either the first cycle or the third cycle of cisplatin and etoposide chemotherapy to determine the optimal timing of TRT for limited-disease small cell lung cancer; Journal of Clinical Oncology, 2012 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 30, No 15_suppl (May 20 Supplement), 2012: 7004
[10] Matthews MJ, Kanhouwa S, Picksen J, et al: Frequency of residual and metastatic tumor in patients undergoing curative surgical resection for lung cancer. Cancer Chemother Rep 1973;4:63
[11] Mountain CF: Clinical biology of small cell carcinoma, Relationship to surgical therapy. Semin Oncol 1978;5:272
[12] Lichter AS, Bunn PA, Ihde DC, et al: The role of radiation therapy in the treatment of small cell lung cancer. Cancer 1985;55:2163
[13] Elliott JA, Osterling K, Hirsch FR, Hansen HH: Metastatic patterns in small-cell lung cancer; Corelation of autopsy findings with clinical parameters in 537 patients. J Clin Oncol 1987;S: 246
[14] Hong S, Cho BC, Choi HJ, Jung M, Lee SH, Park KS, Kim SK, Kim JH.; Prognostic factors in small cell lung cancer: a new prognostic index in Korean patients; Oncology. 2010;79(3-4):293-300.
[15] A. Seegenschmiedt, M.H.; Fessenden, P.; Vemon, C.C. (Eds.) Thermo-radiotherapy and Thermo-chemotherapy, Vol. 1. Biology, physiology and physics, Springer Verlag, Berlin Heidelberg (1996), Vol. 2. Clinical applications, Springer Verlag, Berlin Heidelberg 1996
[16] Urano M, Douple E, (Eds.) Hyperthermia and Oncology. Vol. 1. Thermal effects on cells and tissues, VSP BV Utrecht The Netherlands (1998), Vol. 2. Biology of thermal potentiation of radiotherapy, VSP BV Utrecht The Netherlands (1992) (1998), Vol. 3. Interstitial Hyperthermia: Physics, biology and clinical aspects, VSP BV Utrecht The Netherlands (1992), Vol. 4. Chemo-potentiation by hyperthermia VSP BV Utrecht The Netherlands (1994),
[17] Lindholm CE (1992) Hyperthermia and Radiotherapy. Ph. D. Thesis, Lund University, Malmo, Sweden
[18] Gonzales, G.D.: Thermo-radiotherapy for tumors of the lower gastro-instenstinal tranc., M.H. Seegenschmiedt, P. Fessecden, C.C Vernon (Des.) Thermo-radiotherapy and Thermo-chemotherapy Biology and physics, Springer Verlag, Berlin Heidelberg 1 (1996)
[19] Dewey WC, Hopwood LE, Sapareto SA, Gerweek LE (1977) Cellular Response to Combination of Hyperthermia and Radiation. Radiology 123:463-474
[20] Muller C (1912) Therapeutische Erfahrungen an 100 mit kombination von Rontgenstrahlen un hochfrequenz, resp. Diathermie behandeleten bosartigen Neubildungen. Munchener Medizinische Wochenschrift 28:1546-1549
[21] Hiraoka M, Masunaga S, Nishimura Y, Nagata Y, Jo S, Akuta K, Li YP, Takahashi M, Abe M: Regional hyperthermia combined with radiotherapy in the treatment of lung cancers, Int. J. Radiat. Oncol. Biol. Phys. 22:1009-1014, 1992
[22] Imada H, Nomoto S, Tomimatsu A, Kosaka K, Kusano S, Ostapenko VV, Terashima H: Local control of nonsmall cell lung cancer by radiotherapy combined with high-power hyperthermia using 8MHz RF capacitive heating device, Jap. J. Hyperthermic Oncology, 15:19-24, 1999.
[23] Karasawa K, Muta N, Nakagawa K, Hasezawa K, Terahara A, Onogi Y, Sakata K, Aoki Y, Sasaki Y, Akanuma A: Thermoradiotherapy in the treatment of locally advanced non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 30:1171-1177, 1994
[24] Sakurai H,Hayakawa K, Mitsuhashi Nm Tamaki Y, Nakayama Y, Kurosaki H, Nasu S, Ishikawa H, Saitoh JI, Akimoto T, Niibe H: Effect of hyperthermia combined with external radiation therapy in primary non-small cell lung cancer with direct bony invasion, Int. J. Hyperthermia, 18:472-483, 2002
[25] Hettiga JVE, Lemstra W, MeijerC, Mulder NH, Tonings AWT, deVries EGE, Kampinga HH: Hyperthermic potentiation of cisplatine toxicity in human small cell carcinoma cell line and a cisplatine resistant subline, Int. J. Hyperthermia 10:795-805, 1994
[26] Higashiyama M, Doi O, Kodama K, Yokouchi H: Intrathoratic chemothermiotherapy following

panpleuropneumonectomy for pleural dissemination of invasive thymoma, Chest, 105:1884-1885, 1994
[27] Doi O, Kodama K, Higashiyama M, Kuriyama K, Tateishi R: Postoperative chemothermotherapy fo locally advanced lung cancer with carcinomatous pleuritis, In: Matsuda T. (Ed.): Cancer treatment by hyperthermia, radiation and drugs, Taylor Francis, London, Washington, 1993, Ch 31, pp.338-352
[28] Yang H, Jiang G, Fu X, Liao J: Radiotherapy and hyperthermia for NSCLC, ASCO Annual Meeting, No. 7289, 2005
[29] Kodama K, Doi O, Hagishiyama M, Yokouchi H, Tatsuda M: Long-term results of postoperative intrathoratic chemo-thermotherapy for lung cancer with pleural dissemination, Cancer 72:##, 1993
[30] Xu M, Wright WD, Higashikubo R et al (1996) Chronic thermotolerance with continued cell proliferation. Int J Hyperthermia 12(5):645-660
[31] Smith SR, Foster KR, Wolf GL (1986) Dielectric Properties of VX-2 Carcinoma Versus Normal Liver Tissue. IEEE Trans. Biomed. Eng. BME-33:522-524
[32] Dissado LA, Alison J.M, Hill RM, McRae DA, Esrick MA (1995) Dynamic Scaling in the Dielectric Response of Excised EMT-6 Tumours Undergoing Hyperthermia. Phys. Med. Biol. 40:1067-1084
[33] Szasz A, Szasz N. Szasz O (2010) Oncothermia – Principles and Practices, Springer Scientific, Heidelberg, Dordrecht
[34] Szasz A, Vincze Gy, Szasz O et al (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology 22(2):103–115
[35] Galeotti, T, Borrello, S, minotti, G, Masotti, L (1986) Membrane Alterations in Cancer Cells: the role of Oxy Radicals., Membrane Pathology, Bianchi G, Carafoli E, Scarpa A, (Eds) An. New York Acad. Sci. 488:468-480
[36] Dani A, Varkonyi A, Osvath M, Szasz A: Treatment of non-small-lunk-cancer by electro-hyperthermia, Strahlenter Onko 180:20, 2004
[37] Dani A, Varkonyi A, Nyiro I, Osvath M: Clinical experience of electro-hyperthermia for advanced lung-tumors, ESHO, June 04-07, Munich, Germany 2003
[38] Hager ED, Krautgartner IH, Popa C, Hohmann D, Dziambor H: Deep hyperthermia with short waves of patients with advanced stage Lung Cancer, Hyperthermia in clinical practice, XXII Meeting of ICHS, 1999
[39] Lee DY, Haam SJ, Paik HC, Lim BJ, Kim TH, Kim NY: Complete remission of SCLC with chemotherapy and oncothermia (Case report). Oncothermia J. 2012;5:43-51
[40] Yoon SM, Lee JS: Case of abscopal effect with metastatic non-small cell lung cancer. Oncothermia J. 2012;5:52-57
[41] Szasz A, Szasz O, Szasz N (2006) Physical background and technical realization of hyperthermia. In: Baronzio GF, Hager ED (eds) Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects, Ch. 3., Springer, New York, NY, pp 27-59

Posters of the XXXI. Conference of the International Clinical Hyperthermia Society (ICHS)

You can find more information about our Conference the following website:
www.ichs-conference.org

P-01: Giammaria Fiorentini, Carlo Milandri, Patrizia Dentico, Paolo Giordani, Vincenzo Catalano, Feissal Bunkeila (2012) Deep electro-hyperthermia with radiofrequencies combined with thermo-active drugs in patients with liver metastases from colorectal cancer (CRC): A phase II clinical study

DEEP ELECTRO-HYPERTHERMIA WITH RADIOFREQUENCIES COMBINED WITH THERMO-ACTIVE DRUGS IN PATIENTS WITH LIVER METASTASES FROM COLORECTAL CANCER (CRC): *A PHASE II CLINICAL STUDY.*

Giammaria Fiorentini[1], Carlo Milandri[2], Patrizia Dentico[2], Paolo Giordani[1], Vincenzo Catalano[1], Feisal Bunkeila[1]

[1]Dept. of Oncology Azienda Ospedaliera Marche Nord, Pesaro, Italy
[2]Dept. of Medicine, General Hospital Empoli, Florence, Italy

Purpose

- Increase palliation in patients with liver metastases from CRC
- Evaluate capacitatively coupled low-frequency 13.56 MHz deep hyperthermia combined with thermo-active drugs

Patients and methods

From April 2006 to February 2010, 60 heavily pretreated patients at advanced stage of CRC with not operable liver metastases have been cured with deep hyperthermia at an applied adsorbed power of 80-150 Watt equivalent to 41°- 47° for 60-75 minutes, 3 times/w for 3 weeks in combination with thermo-active drugs.

Thermo active drugs were:

cisplatin 30 mg/sqm on D 1,8, 15 in the first subset of 28 patients (Group A) then with oxaliplatin 50 mgr/sqm on D 1,8,15 in a second subset of 32 patients (Group B). Hyperthermia was achieved by arrangements of capacitative electrodes with a radiofrequency field of 13.56 Mhz (RF-DHT).

RESULTS OF HYPERTHERMIA AND THERMO- ACTIVE DRUGS (60pts)

	Group A CDDP	Group B OXALI	OVERALL	
	28pts	32 pts	60 pts	%
Partial responses	1	5	6	10%
stabilizations	1	5	6	10%
CEA reductions	4	12	16	27%
Increasing performances	11	19	30	50%
Reduction analgesics	5	15	20	33%
Better Q of L	16	34	50	83%

RESULTS OF HYPERTHERMIA AND THERMO-ACTIVE DRUGS (60pts) -TOXICITY

	Group A CDDP	Group B OXALI	OVERALL	
	28pts	32 pts	60 pts	%
Burns G2	3	4	7	12%
Leukopenia G2	1	5	6	10%
Nausea & V. G3	5	4	9	15%
Nefrotoxicity G2	4	0	4	7%
Neurotoxicity G3	1	5	6	10%

RESULTS OF HYPERTHERMIA AND THERMO- ACTIVE DRUGS (60pts)

Group A CDDP	Group B OXALI	OVERALL	%
28pts	32 pts	60 pts	

MEDIAN SURVIVAL TIME

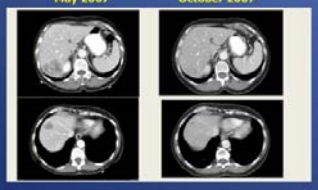
33 weeks (range 19-45)

MEDIAN DURATION OF RESPONSE

19 weeks (range 9-27)

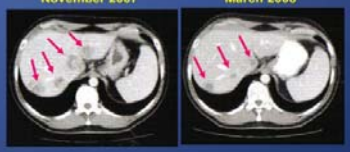
Metastases from CRC: PR lasting 22 weeks

May 2007 October 2007



Metastases from CRC: PR lasting 29 weeks

November 2007 March 2008



Conclusions

Capacitively coupled low-frequency 13.56 deep-HPT is feasible for chemo-refractory malignant liver involvement from CRC. Significant increase of QoL was shown. 12 pts reported a control of disease. Oxaliplatin showed a more effective thermo-enhancement respect cisplatin in liver metastases from CRC. Based on these results and on ethical reasons we abandoned cisplatin and we are planning a further randomized trial comparing FOLFOX 4 plus hyperthermia versus FOLFOX 4. These interesting results deserve to be confirmed in further clinical studies.

P-02: Gramaglia Alberto, Parmar Gurdev, Ballerini Marco, Cassuti Valter, Baronzio Gianfranco (2012) Liposomiated doxorubycyn (LD) and hyperthermia on glioblastoma relapsing after surgery, radiotherapy and two chemotherapy lines: a case report

LIPOSOMIATED DOXORUBYCYN (LD) AND HYPERTHERMIA ON GLIOBLASTOMA RELAPSING AFTER SURGERY, RADIOTHERAPY AND TWO CHEMOTHERAPY LINES: A CASE REPORT

Gramaglia Alberto [1], [*], Parmar Gurdev [2], Ballerini Marco [3], Cassuti Valter [3] and Baronzio Gianfranco [3]

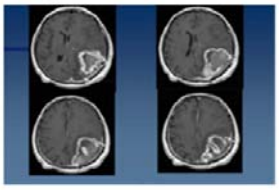
1. Radiotherapy and Hyperthermia Department, Policlinico di Monza, Monza, Italy
2. Integrated Health Clinic, Fort Langley, B.C., Canada.
3. Demetra&Lab Immune, Terni, Italy

Rationale for using liposomal doxorubicin.

Temozolomide is an imido-tetrazine readily absorbed orally and able to cross the blood brain barrier. TMZ has demonstrated activity against Glioblastoma and astrocytoma in various degrees, and in brain metastases (Reardon DA 2006, Addeo R 2011). Although TMZ has become the drug of choice in association with radiotherapy for Glioblastoma, many Glioblastoma patients develop resistance to the drug and become incurable. The complete reasons for why this resistance takes place is at the moment not completely understood, but seems linked to the presence of certain subpopulations of cancer-stem cells inside the tumor mass (Joannensen TC. 2012). This possible and eventual resistance to treatment has forced our group to look for other drugs active on GBM. We have chosen liposomal doxorubicin for various reasons that we will now describe. Liposomal doxorubicin (Caelyx®), is a formulation of hydrochloride doxorubicin wrapped in a film composed by phospholipids and polymers of methoxypolyethylene (mPEG) embedded in the lipid surface (Green AE. 2006). This association provides a favorable pharmacokinetic profile characterized by an extended circulation time, a reduced volume of distribution, thereby promoting an increased tumor uptake (Gabizon A. 2012; Holloway RW. 2010). Tumor abnormal microcirculation and permeability is responsible for the increased uptake and retention of liposomal drugs (Maeda H. 2006). This phenomenon of increased permeability is greatly increased by HT, as demonstrated by Ponce (Ponce AM.2006) and Dvorak (DvorakJ. 2004). Dvorak was one of the first to use the combination of Caelyx® and HT on hepatocellular carcinoma, reporting that the combination of HT and doxorubicin itself may be supra-additive, resulting in enhanced anti-tumor efficacy in the heated region and in decreased toxicity (DvorakJ. 2004). Caelyx® has been investigated by Koukoukaris (Koukourakis MI. 2000) in glioblastoma and in metastatic brain tumours. These authors are in agreement with the Chua and Lesniak group, who have concluded that Caelyx® selectively overcomes the blood brain barrier and accumulates 13-19 times higher in Glioblastoma tissue (Koukoukaris MI.2000; Chua SL. 2004; LesniakMS. 2005). Furthermore, Chua (Chua SL. 2004) has demonstrated the possibilities of using Caelyx® in association with TMZ in recurrent Glioblastoma. Liposomal doxorubicin has been associated with disease stabilization and a modest haematologic toxicity. These studies have convinced our group to test the use of pegylated doxorubicin in recurrent cases of GBM in our clinic. Our initial cases are thus briefly described hereafter.

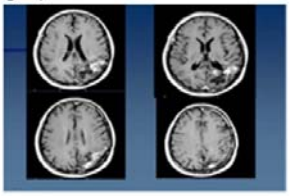
Case of patient treated with Caelyx. The patient (a right handed man) was first surgically treated (December 2005) for left posterior parietal Glioblastoma. The patient then underwent RT (45 Gy CFRT in 18 fractions) followed by a boost CFRT to reduced target (20 Gy in 4 fractions). He then started and continued Temodar (10 cycles) until progression (January 2007). This was followed by 2 cycles of ACNU, until progression (March 2007) (Fig.1). He was then started on Ionidamine and RadiofrequencyHyperthermia(HT). The initial cycles were done at 45 day intervals, then after an initial good response and apparent stabilisation, the GBL progressed the treatment was done at larger intervals of up to 9 CT+HT (the last treatment was done in Nov 2007).

Fig.1



The treatment was as follows: 12 mg/m^2 IV + steroids in glucose solution and on day 1200 mg of Quercetin p.o. one hour before HT, and repeated at least four hours later. From days 2 to 5 the patient underwent 4 consecutive days of more HT and quercetin treatment (100 mg before and after completion of HT).
HT was delivered by means of a 13.56 MHz radiofrequency capacitive device (Synchrotherm Duer) via two opposite plates at the maximum tolerated power for at least one hour for five consecutive days. Due to progression we decided to begin 20 mg of Caelyx® i.v. + HT, with the following schedule: after i.v. injection of Caelyx® an HT application lasting 1 h was done. Following a HT every day were applied for 10 times and a partial regression and stabilization was obtained (Fig..2) .

Fig.2



P-03: Csaba Kovago, Nora Meggyeshazi, Gabor Andocs, Andras Szasz (2012) Proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Csaba Kovago[1], Nora Megyeshazi[2], Gabor Andocs[3], Andras Szasz[4]

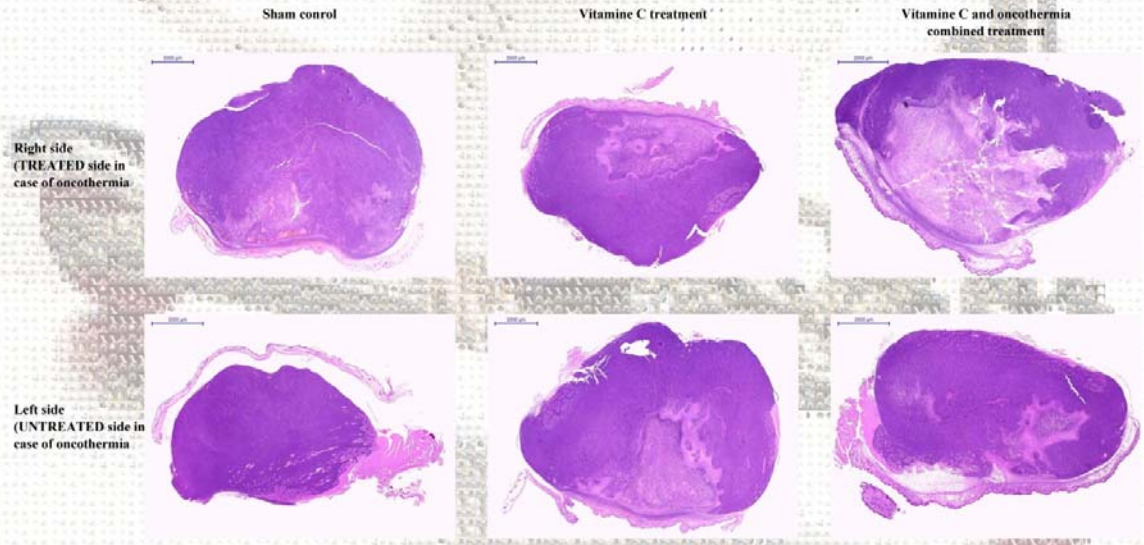
1: Szent Istvan University, Faculty of Veterinary Science, Pharmacology and Toxicology Department, Budapest, Hungary
2: 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
3: Tottori University, Department of Clinical Medicine, School of Veterinary Medicine, Tottori, Japan
4: Szent Istvan University, Faculty of Mechanical Engineering, Biotechnics Department, Gödöllő, Hungary

Introduction - According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in in vitro assays. This fact is a very important using ascorbic acid as complementary drug with standard antitumoral therapy or in cases where currently no other potent treatment is possible. Although the specific method of action is still unclear: high concentration of ascorbic acid produces oxidative shock by H_2O_2 lethal for tumor cells beyond a certain level, however healthy cells can survive the same stress effect.

Objective - The goal of our experiment will be to determine the possible potentiating effect of application of high dose pH-neutralized ascorbic acid to the normal oncothermia treatment method.

Method - The NMRI mice intended to inoculate with C26 Murine Colon Carcinoma cell line subcutaneously at both of their femoral regions and kept till the tumors reach symmetrically the 10 mm in diameter. We plan to create four experimental groups, containing 5 male and 5 female animals in each. The formed groups of animals will be: Gr1. no treatment (control), Gr2. only ascorbic acid treatment, Gr3. only oncothermia treatment, Gr4. both ascorbic acid and oncothermia treatment. Both vitamin-C and oncothermia treatment will be applied once ("single-shut" treatment regime), ascorbic acid will be pH-neutralized and applied intra peritoneal in dose of 2 g/kg bodyweight. Oncothermia treatment will be applied only to the right limb tumor, the other side will be used as internal control. Animals will be held in total anaethesia during the time period of the treatment using ketamine-xylazine combination intraperitonealy (100 mg/bwkg ketamine and 10 mg/bwkg xylazine dose). Oncothermia treatment will be carried out using LabEhy equipment (Oncotherm Ltd, Páty, Hungary), output power set between 5-10 W (to keep the treated tumor core temperarture around 42 °C), treatment time planed to be 30 minutes.
The animals will be sacrificed 48 hours after the treatment, all tumors will be removed and analyzed histopatologicaly. Slides will be stained with hematoxylin-eosin protocol, the slides will be scanned by Pannoramic Scan digital slide-scanner (3DHISTECH Ltd, Budapest, Hungary). The digital images will be analysed by HistoQuant module of the Pannoramic Viewer software (3DHISTECH Ltd, Budapest, Hungary).
The other organs will be routinely checked as well. Our main question centers on the comparison of the cell-destruction ratio of the various applied treatment regimes, and study the possible synergy or additive cross-potentiating of the methods.

Results from a pilot study - The following slides originated from a previously made experiment, to test the idea of the investigation. As it can be seen the combined treatment of vitamine C and oncothermia resulted much larger tumor-tissue death than the vitamine C application alone.



Conclusion - The results of this experiment can help us to plan regimes to potentiate the known effects of the oncothermia methods with fewer side effects than in case of standard complementary chemotherapeutic applications. Our future plan to study further chemical materials, and herbal drugs in the same way in order to determine their possible synergic effects with oncothermia.
Using the results and experiences geathered from this experiment, further investigations are planed targeting herbal and synthetic materials to check the compatibility of these compounds with the effects of the oncothermic treatment.

P-04: Meggyeshazi Nora, Andocs Gabor, Krenacs Tibor (2012) Programed cell death induced by modulated electro-hyperthermia

Programmed cell death induced by modulated electro-hyperthermia

Meggyesházi Nóra[1], Andócs Gábor[2] , Krenács Tibor[1]

[1]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary,
[2]Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

Background: Modulated electro-hyperthermia (mEHT) is a non-invasive technique for targeted tumor treatment. The mEHT generated capacitive coupled modulated radiofrequency selectively accumulates in the tumor tissue without major effect in the surrounding normal tissues.

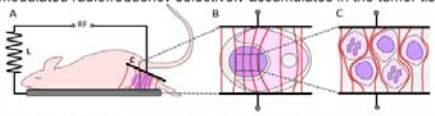


Figure 1: Scheme of the experimental set up and hypothetical effect of modulatated electo-hyperthermia treatment The radiofrequency (RF) generated electric field (red lines) is enriched in the tumor implant which is part of the circuit (A). Cross section through the mid-femoral region filled up by the tumor (violet lump) accumulating the current (B), which can not pass through cell membranes as it is depicted at the microscopic level (C). However, the electric field -alternating by 13.56 MHz- generates heat and interacts with ions in the extracellular space and any dipole molecular groups (non-thermal effect) causing them to rotate both in the matrix and cell membrane receptors. As a result of enhanced electric field and deregulated adaptive pathways in tumors, mEHT treatment can significantly interfere with the fate of tumor cells than normal cells and may trigger tumor cell destruction.

Method: HT29 human colorectal carcinoma cell line xenografted to both femoral region of BalbC/nu/nu mice was treated when reaching ~1.5 cm by using a single shot mEHT treatment (LabEHY, Oncotherm Ltd, Páty, Hungary) for 30 minutes. Sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 h in 3 mice each group by keeping 5 untreated animals. Histomorphologic, immunohistochemical and TUNEL assay results were tested in digital slides and analyzed semi-quantitatively. An apoptosis protein array was used to screen 35 apoptosis releated proteins, results were evaluated using the ImageJ software.

Figure 2: Double tumor model. Temperature (sub-cutaneous, tumor core, control side and rectal) was controlled <43°C.

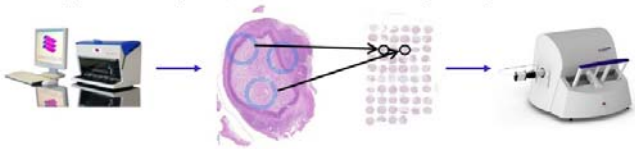


Figure 3: We have prepared tissue microarray (TMA), standard array selection based on digital slides. Followed by several immunofluorescence and immunohistochemistry with TRAIL-R2 , AIF, Cytochrome-C, and cleaved caspase-3 (all from Cell Signaling),and performed TUNEL assay.The slides were digitalised.

Results: mEHT caused programmed cell death related destruction from the tumor centre. TRAILR2 was up-regulated 8h post treatment. Cleaved caspase-3 positive cells appeared only at the tumor periphery between 4-14h. AIF nuclear translocalization at 14h and cytochrome c release from the mitochondria at 8-14h and massive TUNEL positivity at 24-48h indicated DNA fragmentation.

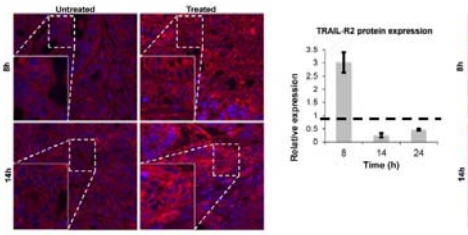


Figure 4. TRAIL-R2 expression in the tumor cell membranes is elevated both 8 and 14 hours post-treatment compared to the control side tumors. The elevation at 14h post-treatment appears only at the tumor periphery but not in the center, while evenly low TRAIL-R2 levels are seen throughout the control tumor. Insets show high power views.

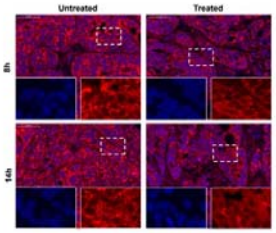


Figure 5: Cytochrome c was released into the cytoplasm from 8h post-treatment with a peak at 14h which disappeared by 24h on the treated sides. It remained mitochondrial in the untreated tumors.

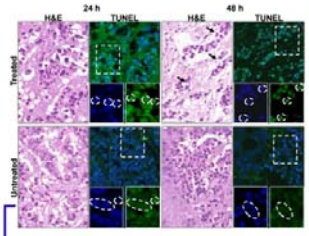
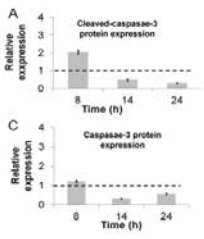


Figure 6: Both nuclear shrinkage and apoptotic bodies (arrows; H&E staining) as well as DNA fragmentation proved by the TUNEL assay (green fluorescence) became significantly elevated both at 24h and 48h after mEHT treatment (upper row) compared to untreated tumors of the opposite legs (lower row). Dashed rectangles highlight representative TUNEL positive areas at higher magnification in insets. Nuclear TUNEL positivity (dashed circles) was verified by showing DNA staining with DAPI in the highlighted identical cells. As a control, other DAPI positive cells particularly in the untreated tumors show only basic green fluorescence levels within dashed oval areas.



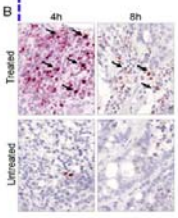


Figure 7: Elevated cleaved/activated-caspase-3 levels detected as early as between 4-8h both in protein arrays(A) and after immunostaining (B) and down-regulation soon afterwards. Low general-expression of non-cleaved caspase-3 was found both in protein arrays (C) and with immuno-histochemistry.

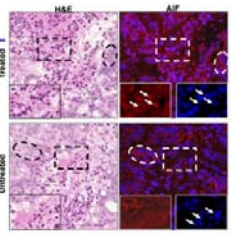


Figure 8: H&E morphology of representative areas of treated and untreated tumors 14 h post-treatment. As an early sign of later DNA fragmentation nuclear translocation of AIF (red) is clearly seen at this stage in the treated side only (dotted square, upper right). This co-localization of AIF (red) and nuclear DNA (blue, DAPI) staining is missing in the untreated control tumor(dotted square, lower right), while the normal mitochondrial AIF is still present. Dotted circles show the normal mitochondrial localization of AIF.

Conclusion: In HT29 colorectal cancer xenograft mEHT (modulated electro-hyperthermia) caused programmed cell death. DNA fragmentation followed rather a caspase independent and AIF dependent subroutine with cytochrome c release.

Acknowledgement: Ivett Teleki, Edit Parsch, Péter Balla, Gergő Kiszner

In memoriam Réka Szász

P-05: Pesti L., Dankovics Zs., Lorencz P., Csejtei A. (2012) Complex treatment of advanced uterine cervix Chemo-radio-thermotherapy case report

Complex treatment of advanced uterine cervix
Chemo-radio-thermotherapy case report

Pesti L., Dankovics Zs., Lorencz P., Csejtei A.
Department of Oncoradiology
Markusovszky Hospital, Non-profit Co.Trust, Vas County, Hungary

Among malignant gynecologic diseases the morbidity of the squamous cell, planocellular carcinoma of uterine-cervix is 1300-1400 cases yearly, with mortality of 500 cases yearly in Hungary [approx. 10 million inhabitants].

We applied complex combination of various treatment modalities in inoperable, or only partially resectable cases:

RADIOTHERAPY (external-beam & brachytherapy) + CHEMOTHERAPY + HYPERTERMIA

Radiotherapy (ionizing radiation) treatment

Teletherapy: CT based radiation with 3D conformity, targeting the pelvic regional lymph-nodes up to 30 Gy; followed by field-concentration in 1-2 steps until 50 Gy, in fractional solution by 2 Gy doses.

Intracavital brachytherapy is applied complementary to teletherapy. After-loading technique is used once a week and three times altogether, providing 6-7 Gy/treatment.

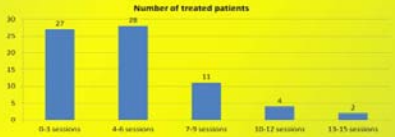
Chemotherapy

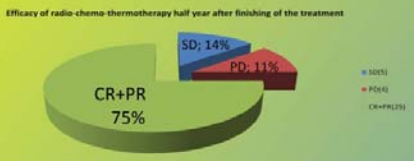
Cisplatin 40 mg/m²/week; concomitantly with tele-radiotherapy.

Local hyperthermia treatment

Complementary to the tele-radiotherapy, two times a week, targeting the pelvis.
Applied energy dose is 45 W, 60 min.
(In days of chemotherapy it is applied just after the infusion.)

We treated 70 patients with uterine cervix malignancies by the above radiotherapy-hyperthermia protocol between 2001 and 2010. All together 331 hyperthermia treatment-sessions were provided for these patients. 34 patients received additional complementary chemotherapy by above dose.





CASE-REPORT (57y old female)

Anamnesis: G2,P2, hypertonia for 15 years, stroke at age 54
vaginal bleeding (23.Dec. 2005), emergency hospitalization in our Department
Diagnose: Neopl.cerv.ut.std IIIB-IV Histology: carcinoma planocellulare kerat.

Teletherapy treatment
Dec.2005 – Feb.2006: external irradiation 2 Gy/day fractions, with 50 Gy complete dose

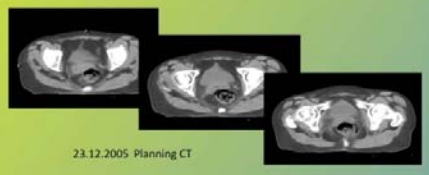
Brachytherapy (after loading treatments)
23.Dec.2005: Block of bleeding, after loading, 8 Gy
05.Jan.2006: After loading, 5 Gy
04.May 2006: After loading 4.5 Gy; targeting the residual tumor

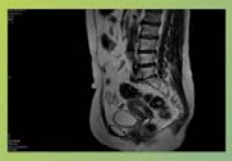
Chemotherapy
Dec.2005 – Feb.2006: 40 mg/m²/week Cisplatin complementary to external radiation

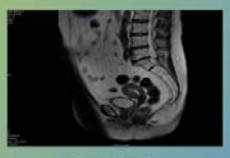
Hyperthermia treatments
Jan. – Feb.2006: 6 sessions
May-Aug.2006: 4 sessions

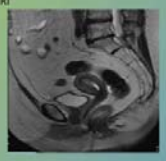
Last pelvic control by MRI: 17.Oct. 2010

NO EVIDENCE OF DISEASE (NED)


23.12.2005 Planning CT


24.03.2006 MRI


13.02.2007 MRI


17.10.2010 MRI

P-06: Peter Lorencz, Andras Csejtei (2012) Experience in the treatment of liver metastases, with special reference to the consequences of interruption of long-run treatments

Experience in the treatment of liver metastases, with special reference to the consequences of interruption of long-run treatments

Peter Lorencz, András Csejtei
Department of Oncoradiology, Markusovszky Hospital, Vas County, Szombathely, Hungary

Introduction: Our department has been dealing with oncothermia since 2001. It is used as one of the complementary treatments which are applied together with the gold-standards. We had treated more than thousand patients with this modality. 80% of the treated patients had primer or metastatic malignant liver tumors. We are intensively studying the long-term application of the hyperthermia, transforming the treatment of malignancy to the same as for one of the chronic-diseases. The cohort which we had chosen received more than 60 oncothermia treatments, and we are studying not only the long-time effects, but the response of long interruption (at least two weeks) of the treatment.

Objective of this presentation: We had chosen a mammary-carcinoma case with liver metastasis to show a typical effect of the interruption of the long-time treatment.

Method: The hyperthermia method was oncothermia, made by the EHY2000 and EHY3000 systems (Oncotherm Kft/GmbH). Oncothermia was applied always complementary to chemo-, radio- or combined therapies. In case of liver no radiation, only chemotherapy was applied. Patients received Oncothermia immediately after the chemotherapy. The control of the patients was made by standard imaging systems (CT, US, MRI).

Case-report: In 2005 a preventive mammography discovered a breast tumor in a female patient born in 1971. In preparation of the surgical intervention the liver metastasis was discovered too.

Applied therapy:

Dec. 22; 2005– breast-keeping surgery, R0

Jan. 2005 – radiotherapy on the breast: 50 Gy
(2 Gy fractioned)+ 10 Gy electron-boost

Jan. 05; 2006 – chemotherapy started (Taxotere + Epirubicine)

Jan. 06; 2006 – oncothermia is planned by CT simulator

Jan. 06; 2006 – Jul.14; 2006 oncothermia
49 sessions (60W, 60 min; 2x/week)

Mar. 06; 2006 – Regression detected by CT

May. 08; 2006 – Regression detected by CT

Sep.15; 2006 – Regression detected by CT

Oct. 18; 2006 – PET/CT negative, NED

Aug. 15; 2007 – NED by CT

No oncothermia is applied at this time

Jun. 06; 2008 – metastasis relapse in liver detected by CT

Jun. 10; 2008 – Chemotherapy (Taxotere +Xeloda)

Aug. 18; 2008 – Chemotherapy (Taxotere + Paraplatin)

Jun. 17; 2008 – Dec. 01; 2008 – 2nd cycle of oncothermia,
24 sessions; 60W.60min; 1x /week)

Jan. 07; 2009 – robust regression by CT

No oncothermia is applied at this time

Jul. 28; 2009 – multiple metastases detected in the liver by CT

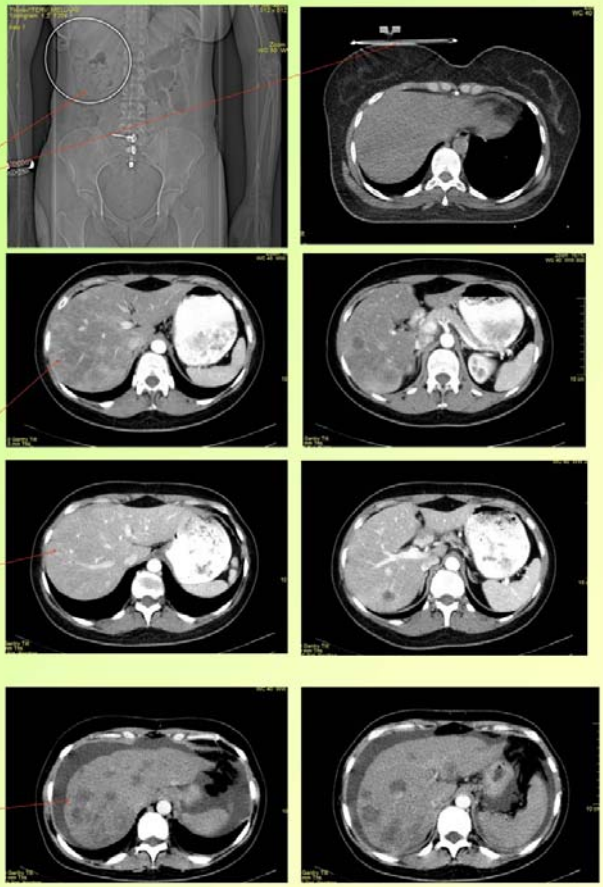
Aug. 12; 2009 – Dec. 18; 2009 – 3rd cycle of oncothermia.
23 sessions; 60W, 60 min; 2x / week

No oncothermia is applied after this time

Sep. 26; 2009 – Chemotherapy (Taxol + Gemzar)

Feb. 08; 2010 – rapid progression detected by CT

Mar. 13; 2010 - exitus



Conclusion: Oncothermia has to be continued while the patient has chemotherapy, or at least until the second negative control (2nd NED).

P-07: Andocs G., Okamoto Y., Osaki T., Tsuka T., Imagawa T., Minami S., Balogh L., Meggyeshazi N., Szasz O. (2012) Oncothermia basic research at in vivo level. The first results in Japan

Oncothermia basic research at in vivo level
The first results in Japan

Andocs, G.[1], Okamoto, Y.[1], Osaki, T.[1], Tsuka, T.[1], Imagawa, T.[1], Minami, S.[1], Balogh, L.[2], Meggyeshazi, N.[3], Szasz, O.[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(2) „Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
(4) Biotechnics Department, Faculty of Engineering, St. István University, Budapest, Hungary

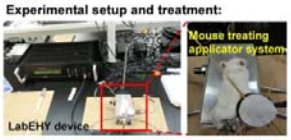
Background: Oncothermia method (OTM) is a long time (since 1989) applied method in oncology.[1] with great clinical success.[2] Oncothermia research group conducts investigations to reveal the basic mechanism of action of this tumor treatment method in basic research level performing a huge number of in vivo studies. The tumor destruction efficacy and the role of temperature independent effects of the OTM was proven earlier and presented elsewhere [3],[4], as well as the recent in vivo results [5],[6]. In this presentation we summarize the first results we have achieved in Tottori University, Japan.

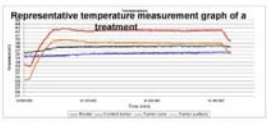
Methods

Study I. :
In the first study we examine the effect of oncothermia treatment in a mouse tumor model.

Animal model: Colon26 (murine colorectal cancer) cell line derived allograft mouse tumor model with double tumors. Every animal had two tumors on the femoral region, the right side (○) was treated, the left side (○) was individual control.

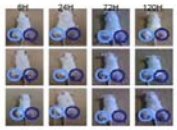
Experimental setup and treatment:





A single shot 30 min oncothermia treatment was done, reaching maximum 41-42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense m3300).

Study design:
Time course study was performed. After a single shot oncothermia treatment animals were sacrificed at 6H, 24H, 72H, and 120H later and tumors were removed. All time-group there were 3 treated animals and 1 untreated control animal.



Tumor sample processing:
All the removed tumors were cut accurately at their centerline. After a standard histological process the samples were stained with HE and TUNEL reaction and Ki-67 detection were performed. Samples were evaluated using complex histomorphological methods.

Study II.:
In the second study we examined the effects of OTM to tumor oxigenization using a rat tumor model.

Animal model: 9L (rat glioma) cell line derived heterotopic allograft rat tumor model with double tumors in both femoral region. Tumor tissue oxigenization was measured in the tumor on the right side.

Oxygen level measurement: pO_2 sensitive elektrode system (Eikon Kagaku Ltd.150D model)

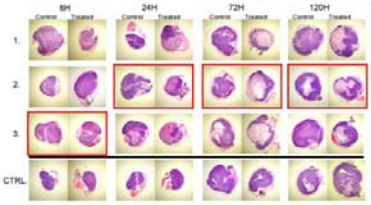
Study design:

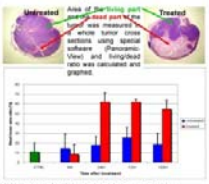
In 11 rats, tumor tissue oxigenization level was measured using a pO2 sensitive electrode system right before the treatment. Then a single shot, 30min oncothermia treatment was performed reaching maximum 42oC intratumoral temperature. Right after the treatment the tumor oxigenization level was measured again.

Results

Study I. :

1. A, Histomorphological changes in a qualitative and a quantitative way:



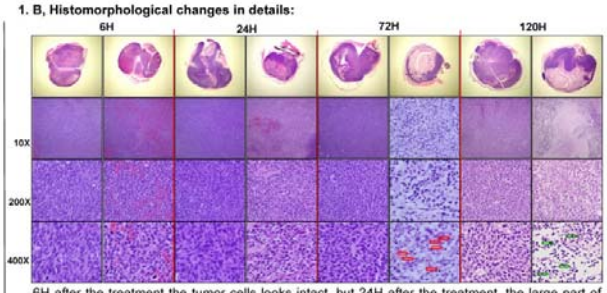


Result graph of the living/dead area ratio measurement of the whole tumor cross sections

Drastic and selective tumor-destruction was detected after a single shot OTM. The tumor destruction was not immediate, it had a time-delay. Samples marked with a red rectangle are evaluated in details.

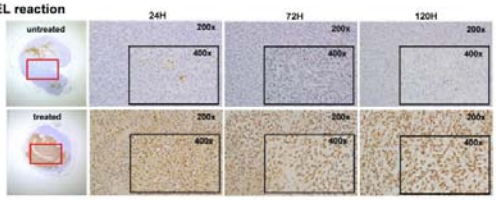
References:
gandocs@gmail.com
[1]Szasz A. (2007) Hyperthermia, a modality in the wings J Cancer Res Ther. 3:56-66.
[2]Szasz A. Szasz N. Szasz O. (2010) Oncothermia. Principles and Practices, Springer Verlag.
(http://www.springer.com/biomed/cancer/book/978-90-481-9487-1?changed=header) Heidelberg, Dordrecht
[3]Andocs G, Szasz O, Szasz A. (2009): Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med. 28(2):148-65.
[4]Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing., Strahlenther. Onkol. Feb;185(2):120-6.
[5] Meggyeshazi N. Programmed cell death induced by modulated electro-hyperthermia. ICHS 2012
[6] Meggyeshazi N. : Early changes in protein expression released to modulated electro-hyperthermia. ICHS 2012

1. B, Histomorphological changes in details:



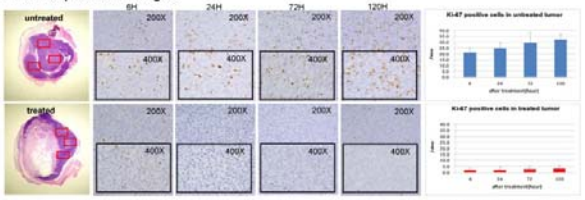
6H after the treatment the tumor cells looks intact, but 24H after the treatment, the large part of the tumor is dead, the cells are shrinked with picnotic cell nuclei. In the 48H and 72H samples definite late morphological signs of apoptotic cell death was observed: extremely high number of apoptotic bodies(▭). 120H after the treatment morphological signs of leukocyte (mostly neutrophiles▭) invasion can be visible.

2.TUNEL reaction



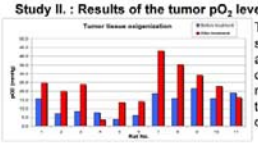
TUNEL assay enzymatically labels the DNA fragments resulted by apoptotic cell death process. In the dead tumor area a huge number of TUNEL-positive cells were observed after a single shot OTM treatment.

3. Ki-67 expression changes

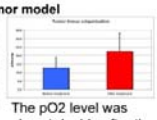


The Ki-67 proliferation marker protein is expressing in the nuclear membrane only in the dividing cells. That is why sampling for Ki-67 positive cell counting was done from the living part of the tumors (▭). In a very interesting way the number of Ki-67 positive cells were significantly decreased in the living part of the treated tumor compared to the control tumors.

Study II. : Results of the tumor pO_2 level measurement in a rat tumor model



Tumor tissue pO_2 level was significantly higher right after the OTM treatment compared the pO_2 level measured right before the treatment in case of 10 out of the total 11 animals.



The pO2 level was almost double after the treatment in average.

Conclusions

1. In the mouse study, OTM treatment can significantly destroy the tumor tissue in a large volume of the tumor even with a single shot way. OTM treatment induces apoptotic cell death in the destroyed tumor tissue and effectively inhibits cell proliferation in the living part of the tumor.
2. In the rat study, OTM treatment can significantly increase the tumor tissue oxigenisation which creates the basis of the strong synergism with radiotherapy and some chemotherapy.

Acknowledgement:

In memoriam Reka Szasz

TATEYAMA KAGAKU GROUP

P-08: Coletta D., Gargano L, Assogna M., Castigliani G., De Chicchis M., Gabrielli F., Mauro F., Pantaleoni G, Pigliucci GM (2012) Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

STABILIZATION OF METASTATIC BREAST CANCER WITH CAPACITIVE HYPERTHERMIA PLUS STANDARD-DOSE CHEMOTHERAPY AND/OR METRONOMIC

Coletta D.[1], Gargano L.[1], Assogna M.[1], Castigliani G.[1], De Chicchis M.[1], Gabrielli F. [2], Mauro F. [2], Pantaleoni G. [2] and Pigliucci G.M. [1]

[1] Department of Oncological Hyperthermia. University of Tor Vergata. Rome. Italy.
[2] Interfaculty Department for Scientific Research (D.I.R.S).- L.U.de.S. University. Lugano – Switzerland.

INTRODUCTION

In our long experience in Universitary Hyperthermia treatment of tumors associated with chemotherapy, we observed that response to associated treatment determines the disease stabilization and significant clinical benefit for 24 months in 12 cases of metastatic breast cancer, whereas chemotherapy alone had shown ineffective with disease progression, bone marrow toxicity G3-4, fatigue G2-3, nausea and vomiting G1-G2, bone pain G3-4 and visceral pain G2-3. (Table 1).

TOXICITY WITH CHT ALONE	TOXICITY WITH ASSOCIATED THERAPIES (CHT+HT)
Bone pain: G3-4	Bone pain: G1-2
Visceral pain: G2-3	Visceral pain: G1
Fatigue: G2-3	Fatigue: G1-2
Nausea and vomiting: G2	Nausea and vomiting: G1
Bone marrow tox: G3-4	Bone marrow tox: G1-2

TAB 1

MATERIALS AND METHODS

2 of 12 patients underwent hormone therapy alone because allergic to chemotherapy drugs, other 10 patients underwent to CHT+/- Hormone Therapy according to the protocols seen in Table 2.

ID	Birth Date	Therapy
C. L.	25/08/1969	*Exemestane*
C. C.	19/02/1947	*CMF, Docetaxel, Nolvadex, Enantone*
D.L.V.	01/05/1956	*Trastuzumab+CBDCA, Myocet+Gemcitabine*
C. P.	22/10/1956	*FEC, Trastuzumab, Vinorelbine, Capecitabine, Fulvestrant*
F. V.	15/03/1946	*Myocet+ Docetaxel, Myocet+Gemcitabine, Zoledronic Acid*
F.D.	20/08/1962	*Fulvestrant+Xeloda, CBDCA+TAX, NVB+GEM*
P.G.	11/12/1957	*Herceptin+NVB, Herceptin,Xeloda*
O.F.	14/09/1959	*Zometa+Tam*
M.D.	19/08/1956	*Xeloda+TXT+BEVA,CBDCA+GEM, TAXOL, NVB, Myocet*
L.G.	28/08/1921	*TXT+Letrozolo*
P.D.A.	24/03/1961	*Herceptin+CBDCA, Myocet+Gemcitabina*
M.C.	19/94/1954	*FEC,CBDCA+GEM, Herceptin+NVB, Lapatinib+Xeloda*

TAB 2

All patients underwent an average 30 cycles of capacitive hyperthermia, each consisting of eight 45-minute sessions every other day, using 300W per session.

RESULTS

In these patients the improvement of performance status has allowed a return to regular life. This improvement of the quality of life showed a correspondent biochemical response, with a progressive reduction in tumour markers and showed also a diagnostic response with stabilization of disease: in some cases reduction of size and/or number of metastases and in all cases with absence of metabolic activity disease (TB PET CT scan).

CONCLUSION 1

The use of OT/CHT-HT combination may enhance efficacy vs CHT and OT alone. This surprising result may confer a small, but probably, clinically significant improvement survival and quality of life. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.

CONCLUSION 2

According to the studies on P.N.E.I.M (1, 6, 7), the results in the field of Clinical Pharmacology concerning drug abuse and medicines disuse, and the resulting recent studies in anthropology on cancer patients, all of our patients were treated at a preventive, therapeutic and post-treatment level with appropriate behavioural tests and drug treatments to avoid relapse. Clinical Pharmacology, in our opinion, considers every patient, according to the multidimensional approach (biopsycosocial), as a global being (8, 9, 10, 11).

REFERENCES

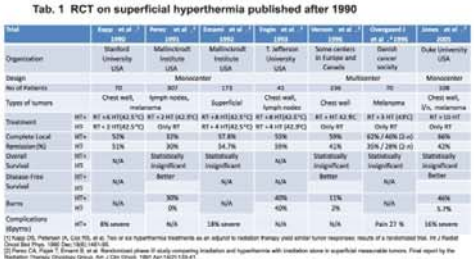
Multidisciplinary therapy for 984 cancer patients:-hyperthermic immunotherapy.
Takeda I, Miyazawa K, Takeda T, Takeda H, Takeda Y
Osaka Cancer Immuno-Chemotherapy Center.
Multidisciplinary therapy for 984 cancer patients: hyperthermic immunotherapy.
Zagar TM, Higgins KA, Miles EF, Vujaskovic Z, Dewhirst MW, Clough RW, Prosnitz LR, Jones EL.
Radiother Oncol. 2010 Dec;97(3):535-40. Epub 2010 Nov 11.
Reirradiation combined with hyperthermia in breast cancer recurrences: overview of experience in Erasmus MC.
Van Der Zee J, De Bruijne M, Mens JW, Arteziano A, Broekmeyer-Reurink MP, Driobal T, Linthorst M, Van Rhoon GC.
Int J Hyperthermia. 2010;26(7):638-45. Review.
Hyperthermia for locally advanced breast cancer
Zagar TM, Oleson JR, Vujaskovic Z, Dewhirst MW, Craciunescu OI, Blackwell KL, Prosnitz LR, Jones EL.
Int J Hyperthermia. 2010;26(7):618-24. Review.
Antiangiogenic metronomic chemotherapy and hyperthermia in the palliation of advanced cancer
Franchi F, Grassi P, Ferro D, Pigliucci GM, De Chicchis M, Castigliani G, Pastore C, Seminara P.
Eur J Cancer Care (Engl). 2007 May; 16(3):258-62.
Immunomodulation, Brain Areas Involved. Daruta Virona. Encyclopedia of Neuroscience. 2009 Part 9, Pages 1925-1929
Neuroendocrine modulation of the immune system: Possible implications for inflammatory bowel disease. Fergus Shanahan and Peter Anton.
Digestive diseases and sciences. Volume 33, Supplement 3 (1988), 41S-49S.
The Holistic Claims of the Biopsychosocial Conception of WHO's International Classification of Functioning, Disability, and Health (ICF): A Conceptual Analysis on the Basis of a Pluralistic–Holistic Ontology and Multidimensional View of the Human being.
Hans Magnus Solli and Antonio Barbosa da Silva. J Med Philos first published online May 7, 2012 doi:10.1093/jmp/jhs014.
Self-criticism, neediness, and distress among women undergoing treatment for breast cancer: A preliminary test of the moderating role of adjustment to illness.
Campos, Rui C.; Besser, Avi; Ferreira, Raquel; Blatt, Sidney J.
International Journal of Stress Management, Vol 19(2), May 2012, 151-174. doi:10.1037/a0027996
The psychological impact of mammographic screening. A systematic review.
J. Brett, C. Bankhead, B. Henderson, C. Watson, and J. Austoker
Psycho-Oncology, vol. 14, no. 11, pp. 917–938, 2005.
Anxiety, emotional suppression, and psychological distress before and after breast cancer diagnosis.
Y. Iwamitsu, K. Shimoda, H. Abe, T. Tani, M. Okawa, and R. Buck
Psychosomatics, vol. 46, no. 1, pp. 19–24, 2005.

P-09: Sergey Roussakow (2012) Critical analysis of randomized trials on electromagnetic hyperthermia: doubful effect and multiple biases

CRITICAL ANALYSIS OF RANDOMIZED TRIALS ON ELECTROMAGNETIC HYPERTHERMIA: DOUBTFUL EFFECT AND MULTIPLE BIASES

Sergey Roussakow, PhD
Galenic Research Institute for Non-Specific Pathology, Moscow

Tab. 1 RCT on superficial hyperthermia published after 1990



Tab. 2 RCT on deep hyperthermia published after 1990

INTRODUCTION

Hyperthermia in oncology had been extensively studied since 60th. Despite of more than 13 000 publications, 50 monographs and manuals and more than 1 200 clinical trials, hyperthermia is still not accepted as a regular cancer treatment. The current trial was performed for further explanation of this situation.

METHODS

All the available randomized controlled trials (RCT) on hyperthermia (HT) in oncology published after 1990 were studied: 7 RCTs on superficial HT (Tab. 1), 6 RCTs on deep loco-regional HT (Tab. 2) and 1 RCT on whole-body HT (altogether 14 RCTs). All the RCTs were studied from the position of "null hypothesis", i.e. considering HT not effective and/or not safe. These were analysed for 1) efficacy by clinical outcomes, 2) toxicity, 3) biases.

RESULTS AND DISCUSSION

8 of the 14 RCTs were recognized as negative by their authors (Tab. 3). HT significantly improved survival in 2 RCTs only. In other trials, HT didn't effect survival significantly, sometimes worsening it. Improvement of local control was the only significant and permanent effect of those positive RCTs. Careful analysis of all the positive RCTs revealed significant biases (Tab. 4) which affected their results.

Inadequate comparator was the most common bias. Typically this was a low-dose radiotherapy (RT) (Overgaard, 1996; van der Zee, 2000; Harima, 2001). As a result, clinical effect in HT-groups of the trials was worse than in other trials, where adequate RT doses (without HT) was used. Toxicity and expensiveness of thermoradiotherapy (TRT) were higher than of RT alone. Therefore, results of HT RCTs received with inadequate comparator were clinically insignificant. At the same time, HT worsened clinical outcomes when applied vs. adequate control (standard high-dose RT). At least in one case HT with adequate RT control significantly reduced overall survival (Vasanthan, 2005) (Fig. 4). Comparative analysis allows to hypothesise, that improvement of local control in the trials with inadequate comparator was achieved for account of significant decrease of overall survival in comparison with trials with adequate treatment (Fig. 3). Significance of RT dose was clearly demonstrated in the RCT of Overgaard et al. (1996) (Fig. 1): increase of RT dose for 10% led to 120% increase of 2-year local control rate, though effect of HT was 2 times less (60% only).

In Jones et al. (2005) trial, defect of randomization was revealed. As a result, RT dose in HT group was 10% higher than in the control RT group (55 Gy vs. 50 Gy). This difference can explain the received clinical effect in full. Additionally, pre-selection of thermosensitive patients was applied in this trial, though the conclusions of the trial were not limited to thermosensitive patients only. Clinical effect in Harima et al. (2001) trial also could be explained by pre-selection of aged patients (median age in HT group of previously untreated patients was 65 years, though the expected age of the first diagnosis is 55 years) and inadequate RT dose to tumor mass (60.6Gy). It's well known that local control after HT is much better among aged patients (Fig. 2).

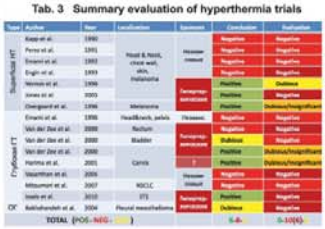
Some trials were incorrectly designed. In Vernon et al. (1996) trial, some different trials were combined in order to reach statistical significance level. Overgaard et al. (1996) trial was experimentally designed. In van der Zee et al. (2000) trial, different protocols were used which are impossible to average. Incomplete data presentation and inadequate analysis are typical biases.

In Issels et al. (2010) trial, systematic distortion in favor of HT group was revealed. As a result, intensity of base therapy in control group was twice lower than in HT group. This distortion excessively explains the received clinical effect without necessity of HT hypothesis. Also, the best results in HT group were much worse than those reported in meta-analysis of 14 earlier RCTs (without HT). This allows to hypothesise that HT possibly worsened the clinical results instead of improve them. This hypothesis is supported by the rise of toxicity in HT group. General toxicity rose 9 times and severe toxicity (treatment-limiting) rose 20 times vs. toxicity in the control group.

The only existing RCT on whole-body HT showed that HT significantly and strongly worsened clinical results comparatively with chemotherapy alone (Fig. 5).

All the RCTs considered as positive by their authors were sponsored by different hyperthermic societies. All the RCTs sponsored by independent organizations were negative.

Tab. 3 Summary evaluation of hyperthermia trials



Tab. 4 Evaluation of biasses in positive RCT

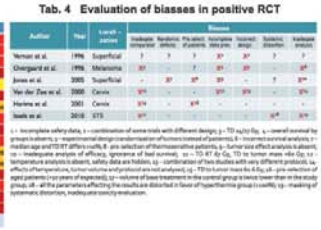
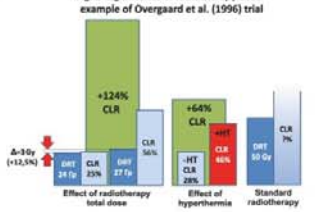
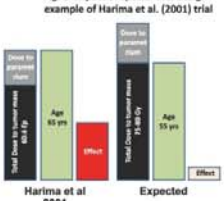


Fig. 1 Significance of radiotherapy dose - example of Overgaard et al. (1996) trial



2 year complete local remission rate (CLR) in the group with total dose (TD) 27Gy was 56% vs. 25% at TD=24Gy (+124%, p<0.05). Therefore, impact of TD for CLR was twice stronger that hyperthermia impact (CLR+46% in hyperthermia group vs. 28% in the control group, +64%). Obviously, with standard TD of DRT (50Gy) the effect of thermal potentiation would be statistically insignificant.

Fig. 2 Impact of special trial design - example of Harima et al. (2001) trial



- **Inadequate control** (TD to tumor mass 60.6 Gy vs. 75-80 Gy with adequate radiotherapy) allows to show effect of thermal potentiation
- **Relatively high dose to parametria** (21.6 Gy or ~25% TD) makes impression of adequate TD (82.2 Gy), reduces relapses rate and makes better survival
- **Pre-selection of aged patients** (+10 years vs. expected age of 1st diagnosis) makes local control better.

Fig. 3 Comparison of RCT on cervix cancer

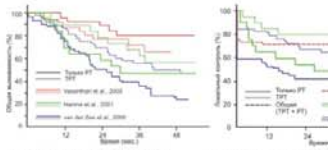


Fig. 4 Decrease of survival in HT group (Vasanthan, 2005)

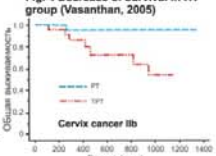
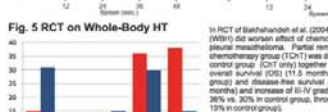


Fig. 5 RCT on Whole-Body HT



In RCT of Bakhshandeh et al. (2004), whole-body hyperthermia (WBH) did worsen effect of chemotherapy (CHT) in malignant pleural mesothelioma. Partial remission (PR) rate in thermo-chemotherapy group (TCHT) was decreased to 18% vs. 31% in control group (CHT only) together with significant decrease of overall survival (OS) (11.5 months vs. 15 months in control group) and disease-free survival (DFS) (5.6 months vs. 9.2 months) and increase of III-IV grade toxicity (neutropenia (NP) 36% vs. 30% in control group, thrombocytopenia (TP) 38% vs. 15% in control group).

Bakhshandeh A, Mosalaeinoori G, Zabel P, et al. Randomized trial with ICE (fosfamide, carboplatin, etoposide) plus whole body hyperthermia versus ICE chemotherapy for malignant pleural mesothelioma. //Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post Meeting Edition). Vol. 22, No. 14S (July 15 Supplement), 2004: 7288.

ABSTRACT

Hyperthermia in cancer treatment still remains an experimental treatment without real clinical future. For further explanation of this situation, all the available randomized clinical trials (RCT) on electromagnetic hyperthermia (EMHT) were studied from the position of 'null hypothesis', taking into account the probable biases. The careful analysis hasn't confirmed a clinical efficacy of EMHT despite of its type: superficial, deep (locoregional) or whole-body. There is no any positive trial not affected with serious biases. After adjustment to the biases, there is no any trial with significant effect of EMHT. EMHT efficacy was shown either in trials with experimental design or versus incorrect comparator. In clinical setting and with correct comparator, EMHT was ineffective or not enough effective to counterbalance its obvious limitations – toxicity and labor-intensity. Since EMHT doesn't generally improve the results obtained with standard effective treatment protocols but significantly increases toxicity, its usefulness is doubtful in general, because an equal or even better effect could be obtained by applying a standard high-dose protocols of radiotherapy or chemotherapy, with lower toxicity and significantly lower labor costs.

Publication: 1. Reported on XXX annual ICHS meeting (Tbilisi, 9-11 сентября 2011 г.)
2. Submitted to «Medical Radiology and Radiation Safety» Journal

P-10: Strauss CA., Kotzen JA., Baeyens A., Mare I. (2012) Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

Oncothermia in HIV Positive and Negative Locally Advanced Cervical Cancer Patients in South Africa

C-Therm Africa
Your partner in oncologic hyperthermia

Strauss C.A., Kotzen J.A., Baeyens A., Maré I.
University of the Witwatersrand
Medical School, Radiation Sciences

INTRODUCTION:

The investigation of technologies which can increase cancer treatment efficacy is driven by:

- The high prevalence of Human Immunodeficiency Virus (HIV) and cervical cancer in South Africa [1 2]
- The growing concerns that HIV infection and certain Antiretroviral Therapies (ARTs) increase the sensitivity to radiation therapy (RT) and chemotherapy, [3 4 5]
- The economic impact of cancer on the already over-burdened healthcare system and economy in Africa [6]

AIM: To investigate the clinical and economic benefits of the addition of oncothermia to standard treatment protocols for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa and to study the radiosensitising effects of the technology on a cellular level in these patients.

OBJECTIVES

PRIMARY:

Evaluate the effect of the addition of oncothermia on:

- Local disease control at 6 months (assessed by PET scans);
- Progression free survival at 12, 18 and 24 months;
- Overall survival at 2 years (and the cause of death)

SECONDARY:

- Evaluate adverse effects that can be directly attributed to oncothermia
- Evaluate the effects of oncothermia on tolerability and toxicity of the prescribed treatments
- Evaluate the economic impact of the addition of oncothermia in public healthcare (based on quality adjusted life years)
- Evaluate the effect of the addition of oncothermia on the quality of life of patients
- To evaluate the effect, if any, of oncothermia treatments on the HIV disease status of HIV positive participants as assessed by:
  - CD4 count
  - HIV viral load
  - Concurrent AIDS-defining conditions
- To describe cervical cancer recurrence patterns in both groups

RADIOBIOLOGY RESEARCH

- To evaluate thermoradiosensitivity by measuring DNA damage (double strand breaks), using Micronucleus (MN) assays, in response to ionising radiation combined with oncothermia before and after completing treatment in HIV positive and negative patients.
- To investigate the molecular markers for thermoradiosensitivity. This will be done by comparing gene expression profiles of cells extracted from biopsies of thermoradiosensitive and thermoradioresistent tumours. Gene profiling of tumour samples will be used to identify potential molecular markers in the tumour cells which are associated with increased response or with resistance to radiochemotherapy combined with oncothermia. This may eventually result in individualised treatment schedules and may be useful in separating patients with and without recurrence following oncothermia.

METHODOLOGY:

Study Type: Phase III randomised clinical trial. Sample: 236 HIV negative and HIV positive stage IIb-IV locally advanced cervical cancer patients will be recruited. This is based on the estimated required sample size for a two-sample comparison of survivors' functions at two years. The statistical significance is defined as a two-sided alpha<0.05 for a log-rank test, with a constant Hazard ratio of 0.5693, a statistical power of 90%, a 15% withdrawal rate and an estimated 140 events. We anticipate at least 50% of recruited participants will be in Stage III of the disease and around 30% of these participants will be HIV positive. Randomisation: The participants will be divided into a control group (N=118) and a study group (N=118) and the sampling method used will be stratified random sampling (stratum: HIV status). In each stratum there will be a random selection in order to ensure equal numbers of HIV positive and HIV negative women in each group. Location: The trial will be conducted at the Charlotte Maxeke Johannesburg Academic Hospital, Gauteng, South Africa. Treatment: Participants from both groups will receive 3 doses of cisplatin (80mg/m^2), external beam radiation (50Gy administered over 25 factions of 2Gy) and 3 HDR intracavitary brachytherapy treatments of 8Gy each. The study group will receive two 60 minute oncothermia treatments per week during the external beam radiation therapy. Duration: The study is scheduled to start in January 2013 and the recruitment is expected to take two years. Participants will be monitored for two years after completion of the treatment protocols. The total study duration is therefore expected to be 4 years.

EXPECTED OUTCOMES:

- The addition of oncothermia to standard treatment protocols will result in improved local disease control and two year survival rates in HIV positive and negative locally advanced cervical cancer patients without increasing the treatment toxicity.
- We hypothesise that the addition of oncothermia will result in a reduction in healthcare costs associated with the treatment of cervical cancer. This would significantly benefit the already over-burdened healthcare system and economy of South Africa and other developing countries.

ACKNOWLEDGMENTS: The EHY 2000 Plus device which will be used for the trial is being supplied by Oncotherm GmbH

References

1 UNAIDS (2009) **South Africa** (Accessed July 2012) Available online from: http://www.unaids.org/en/regionscountries/countries/southafrica/
2 National Cancer Registry of South Africa (2010) **2001 National Cancer Registry Tables** Published in Cancer in South Africa, 2000-2001;
3 Mallik S., Talapatra K., Goswami J. (2010) **AIDS: a radiation oncologist's perspective** *Journal of Cancer Research and Therapeutics* Vol. 6, No. 4, pp: 432-441
4 Baeyens A., Slabbert J.P., Willem P., *et al.* (2010) **Chromosomal radiosensitivity of HIV positive individuals** *International Journal of Radiation Biology* Vol. 86, No. 7, pp: 584-592
5 Ousri N., Yarchoan R. and Kaushal A., (2010) **Radiotherapy for patients with the human immunodeficiency virus: are special precautions necessary?** *Cancer* Vol. 116, No. 2, pp: 273-283
6 American Cancer Society (2007) **Global Cancer Facts & Figures 2007**, pp:8; 23,

P-11: Jückstock J., Eberhardt B., Kirchner H., Müller L., Sommer H. (2012) Locoregional hyperthermia combined with chemotherapy for metastatic breast cancer patients – preliminary results of the Mammatherm-trial

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

CAMPUS INNENSTADT

KLINIK UND POLIKLINIK FÜR FRAUENHEILKUNDE UND GEBURTSHILFE

Locoregional hyperthermia combined with chemotherapy for metastatic breast cancer patients – preliminary results of the Mammatherm-trial

J. Jückstock[1], B. Eberhardt[2], H. Kirchner[3], L. Müller[4] and H. Sommer[1]

[1]Klinikum Innenstadt, Munich University, Gynecology and Obstetrics, Munich, Germany
[2]Kreiskrankenhaus Landshut-Achdorf, Gynecology and Obstetrics, Landshut, Germany
[3] Onkologische Schwerpunktpraxis Leer-Emden, Leer, Germany
[4] KRH Klinikum Siloah, Hannover, Germany

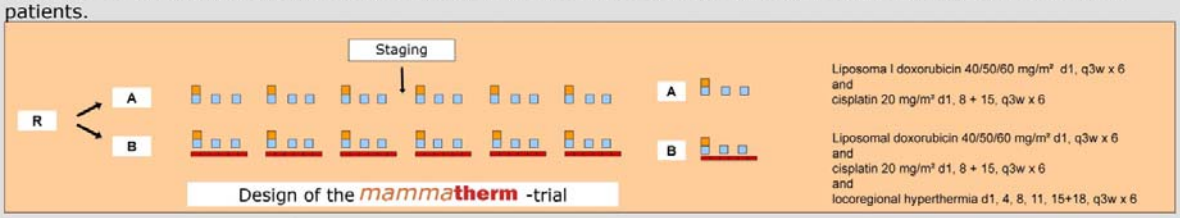
LMU

mammatherm

NOGGO

Background

Treatment options for patients with metastatic breast cancer should be as effective and preferably as little toxic as possible. To date there is no standard therapy available and treatment regimens for metastatic breast cancer vary largely. Locoregional hyperthermia might show additive effects to chemotherapy due to an increased perfusion and a simultaneous occurrence of interstitial acidosis in tumor tissue. In randomized clinical trials the addition of hyperthermia to radiation in advanced breast cancer was associated with improved outcome. To our knowledge so far there are no randomized clinical trials evaluating the effect of a combination of hyperthermia and chemotherapy in breast cancer patients.



Design of the mammatherm -trial

Fig. 1: Hyperthermia devices in the study

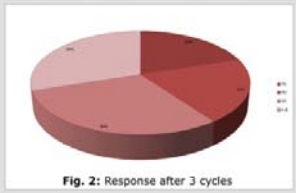


Fig. 2: Response after 3 cycles

Patients and Methods

Phase I of the multicenter German Mammatherm-trial was a dose-finding-study for liposomal doxorubicin administered in combination with cisplatin (20mg/m2) and locoregional hyperthermia. Patients received 6 cycles of therapy according to the following regimen:
liposomal doxorubicin 40 or 50mg/m2 i.v. d1 q22d and cisplatin 20 mg/m2 i.v. d1, 8, 15 q22d in combination with locoregional hyperthermia administered at d1, 4, 8, 11, 15, 18 q22d. Dosage escalation levels for liposomal doxorubicin were at 40/50mg/m2; an escalation up to 60mg/m2 was planned but not effected due to dose limiting toxicities (DLTs).
DLTs were defined as non-hematological toxicities > grade 2 NCI CTCAE (National Cancer Institute Common Terminology Criteria of Adverse Events), - except of nausea and vomiting -, or hematological side effects grade 3 or 4 NCI CTCAE leading to treatment postponement of more than 7 days, if those adverse events were at least possibly associated with the study therapy.
Here first results of the trial concerning the observed DLTs are presented.

Results

A total number of 10 patients were recruited into the trial between August 2007 and May 2011. The therapy was prematurely stopped in 6 patients. Therapy was discontinued in only one patient due to toxicity (adiponecrosis); all other discontinuations were required because of tumor progression. Dose limiting toxicities (DLTs) were observed in 2 patients and comprised liver toxicity in a patient with liver metastases, and, probably, but not proven, tumor-associated bone pain. A causal link to the administered chemotherapy could not be ruled out but appeared to be rather unlikely in both cases. None of these adverse events required treatment discontinuation. There were neither hematological nor hyperthermia related DLTs seen.

	grade 3	grade 4
leukopenia	6	
Neutropenia	3	
thrombopenia	-	
anemia	-	
GOT ↑		1
GGT ↑		1
Total of non-hematological toxicity	12	2
Burns	1	
SAE's	6	

Table 1: Incidence of grade 3/4-toxicities

Conclusion

The combination of locoregional hyperthermia and chemotherapy in pretreated metastatic breast cancer patients showed a tolerable toxicity profile. Data concerning the final toxicity analysis are pending.

12. Conference of the International Clinical Hyperthermia Society• Budapest, October 2012• Dr. Julia Jückstock
Klinikum Innenstadt Munich University, gynecology and obstetrics • Munich, Germany • julia.jueckstock@med.uni-muenchen.de

P-12: Oliver Szasz, Gabor Andocs, Nora Meggyehazi, Andras Szasz (2012) Oncothermia – personalized treatment option

Oncothermia - personalized treatment option

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]

(1) Department of Biotechnics, St. Istvan University, Hungary

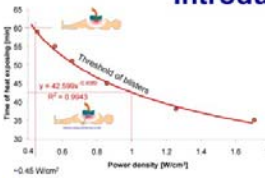
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

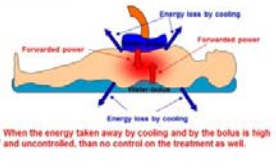
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Objective

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment by tuned energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3], and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized. [5]

Introduction

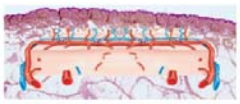


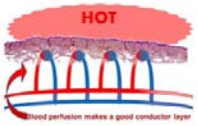


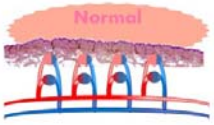
When the energy taken away by cooling and by the bolus is high and uncontrolled, than no control on the treatment as well.

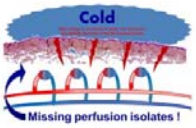
Discussion

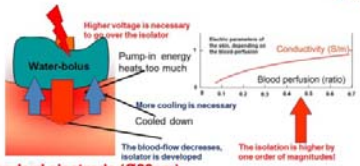
The main factor of the homeostatic control is physiological, based on the active homeostatic control of the blood-perfusion and blood-flow regulating the energy-intake and heat-exchange in the target. The high blood-flow is an effective heat-exchanger, cools the given volume. The well conducted treatment optimizes the current flow-density through the lesion, and optimizes the treatment. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. This regulation is also stress dependent, and depends on the human race-variants as well. The step-up heating is important not only avoid the inconveniences, but regulate the adaptation mechanisms. Healthy cells can be adapted to the electric/heat-stress, while this adaptation is much less in the malignant lesions. The applied step-up heating supports the physiological selection and makes the contrast of the reaction definite. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed for all the deep-seated treatments of various organs.

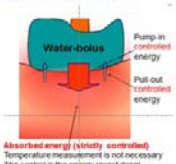








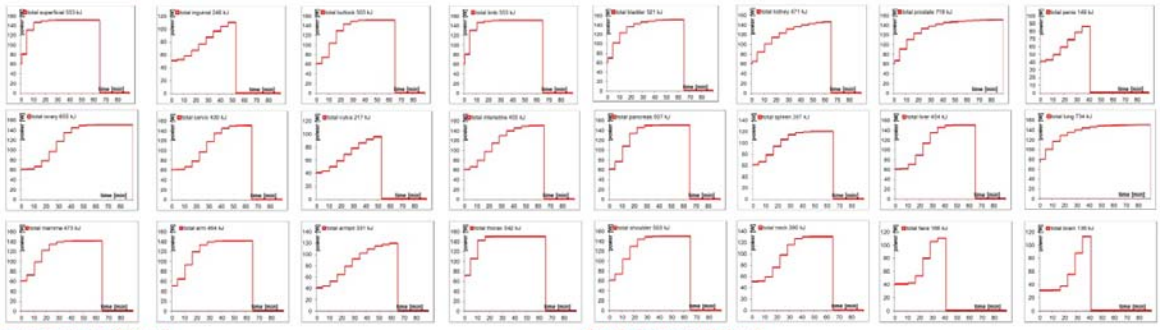




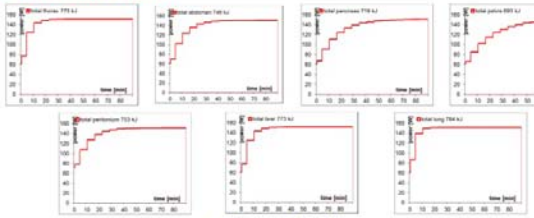
This patented technique makes possible

- ✓ Temperature measurement is not necessary, the energy control is valid
- ✓ We get the highest available RF-current, which does the decisional effect
- ✓ Oncothermia is extraordinarily safe and effective
- ✓ It is possible to make special protocol proposals for general use, and it modified by patients needs

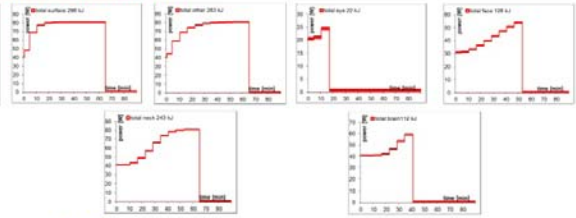
Standard electrode (Ø20cm)



Large electrode (Ø30cm)



Small electrode (Ø10cm)



Conclusion

Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes possible the accurate and personalized treatment by this method.

In memoriam Reka Szasz

References

[1] Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and Practices, Springer, Heidelberg, Dordrecht
[2] Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165
[3] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro- biology 22:103-115.
[4] Meggyeshazi N. et al, Virchov Conference, Prague… Sept. 2012
[5] Neber DW, Zhang G (2012) Personalized medicine: Temper Expectations, Science 337:910

P-13: Gabor Nagy, Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Deep temperature measurements in oncothermia processes

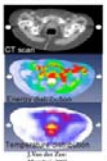
Deep temperature measurements in oncothermia processes

Gabor Nagy[1], Oliver Szasz[1,2], Gabor Andocs[3], Nora Meggyeshazi[4], Andras Szasz[1,2]

(1) Oncotherm GmbH/, Troisdorf Germany & Oncotherm Kft, Paty, Hungary
(2) Department of Biotechnics, Faculty of Engineering, St. István University, Budapest, Hungary
(3) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(4) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

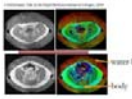
Introduction

The controlled and focused heat-delivery to deep-seated tissues is a long-standing problem of the local hyperthermia in oncology. [1]. The multiple artificial methods to focus the temperature has numerous technical and physiological problems. The energy could be focused in planned accurate way, but the temperature is naturally spread, as well as the physiological controls likely contra-effects the actual heating process. Our objective is to show how oncothermia makes the energy delivery in controlled way in depth.

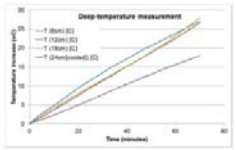


Electric Tea Kettle – 1300 Watts is boiling 2 cups of water in about 3 minutes from room temperature. Most of the hyperthermia devices with same energy heat up the same volume of tissue from 36°C to 43°C during 60 minutes

The energy-pattern far not correlates with the temperature pattern of the same treatment. The reason is the various blood-flow in the regions. (van der Zee, Conference in Mumbay 2005

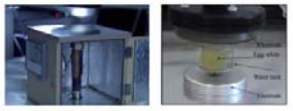


Many times the bolus is heated up more than the desired tissue

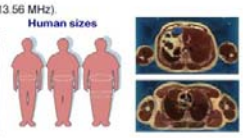


Method

The heating method is impedance –heating with modulated RF (13.56 MHz).



The RF-impedance heating easily heats up the loads to high temperature, and even coagulates the egg-white (without heating up the surrounding water).

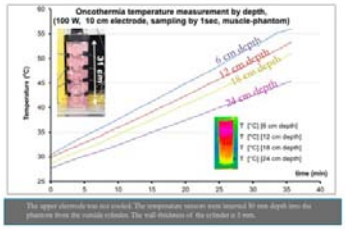


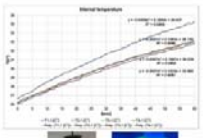
Human "thickness is ranging between 25-32 cm in average in lying-position

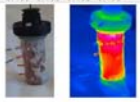
Applied equipment was EHY2000 device

We measured the temperature in various systems, starting with muscle phantoms and with experimental in-vivo models, preclinical (veterinarian) cases and in human applications too. The early (twenty years old) phantom measurements were repeated by more modern conditions, and were checked with optical fiber thermo sensing method, as well as the outside heating profile was controlled for visual pattern by high-sensitivity thermo-camera system. The in-vivo models as well as all the animal experiments had used flouroptical temperature measurements in depth. The precise inserting of the sensors was controlled by imaging technologies in large animals and humans.

Impedance heating; (current flows through)

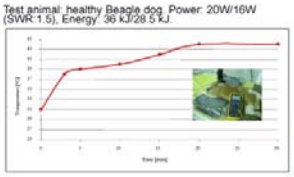




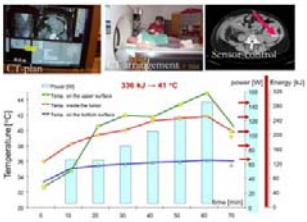


Measurements in physiological conditions

Test animal: healthy Beagle dog. Power: 20W/16W (SWR:1.5), Energy: 36 kJ/28.5 kJ.

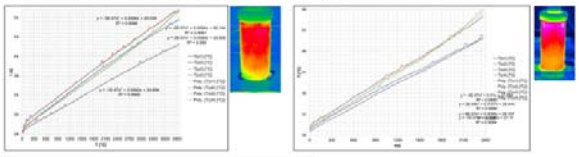


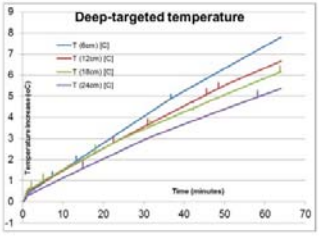
Treatment of tumorous dog



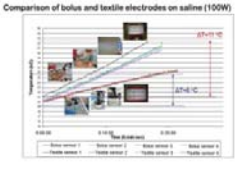
Results

The experiments in phantoms shown a well increased temperature (at least 7 C in depth of 24 cm by 100 W in 60 min applied the 10 cm diameter bolus electrode) [2]. The animal experiments had shown the easy heating the tumor lesion to 42°C without heating the surrounding tissue [3]. The human probes had shown the desired temperature increase in depth, [4], [5]. Important observation is the safe application, no erythema or other dermatological toxicity was caused by the deep heating. This observation is supported by the fact, that the huge number of oncothermia applications worldwide (over 100.000 treatments/year) is free from toxicity or severe skin complications. Only approx. 3% of the all treatments causes light erythema, which could be eliminated by appropriate greasy cream for next day. Parallel with the overall temperature increase the active nano-heating is well measured reaching huge temperature gradient at the membranes of the malignant cells [5].





Heating in depth. 60W applied on 25 cm phantom (above) and 100W for 30 cm phantom .



Conclusion

Oncothermia is effective deep heating method for tumor-lesions, increasing the temperature by safe, controlled and well-targeted way.

References

[1] Segenschmiedt MH, et al.: Thermoradiotherapy and Thermochemotherapy. Berlin, Springer-Verlag, vols. 1, 2, 1995
[2] Nagy G. (2012) unpublished data, Oncotherm Kft, Paty, Hungary
[3] Andocs G (2012), unpublished data, Tottori University, Japan
[4] Szasz A (2008) Hyperthermie/Oncothermie – Ein verlässliches Werkzeug in der Behandlung fotge-schrittener Krebserkrankungen. Neueste forschungsergebnisse. Oncology Dialog, pp. 6-21.
[5] Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and Practices, Springer, Heidelberg, Dodtrecht
[6] Cooper TE and GJ Trezek. Correlation of thermal properties of some human tissue with water content. Aerospace Med. 42, 24-27, 1971

In memoriam Reka Szasz

P-14: Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Oncothermia paradigm

Oncothermia paradigm

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]

(1) Department of Biotechnics, Faculty of Engineering, St. István University, Budapest, Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

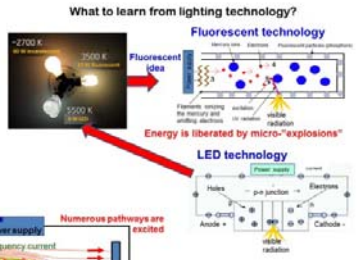
Objective

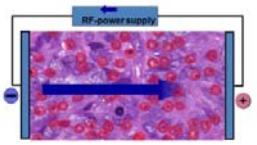
Oncothermia is a new type of cancer-treatment targeting the malignant cells on nano-range, at its membrane and exciting basic cellular signaling pathways, [1]. The front-line achievements explaining the cellular differences between malignant and healthy cells were well recognized in the last century, but unfortunately these were not used for selection in practical applications. Our objective is to show how oncothermia uses these brilliant and strongly proven results.

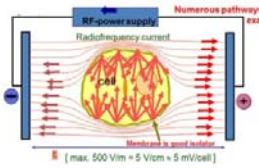
Philosophy of Oncotherm Research and Innovation

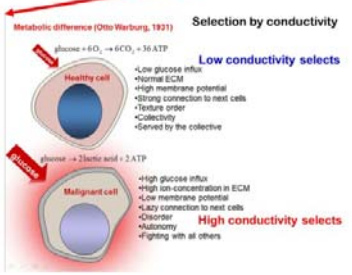
Method

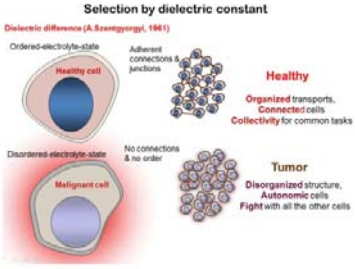
Oncothermia excites many signaling pathways by electric field and huge temperature gradient at the cellular membranes.
The selection of the cells are based on three strong discoveries:
High glucose metabolism of malignant cells discovered by Nobel-laureate O.Warburg [2]. This creates special extracellular conditions around the malignant cells in comparison to their healthy counterparts.
Definite dielectric differences of the malignant (alpha state) and normal (beta-state) cells, discovered by the Nobel laureate A.Szentgyorgyi [3]. This idea is extended by the beta-dispersion selection, [4], and effectively used for membrane excitations
The structural differences (distinguishing by the pathological patterns) can be described with fractals is space and their dynamism by fractals in time. This called "fractal physiology", [5], which distinguishes between the tissues, recognizing the individual, autonomic cells from the collective, correlated ones.

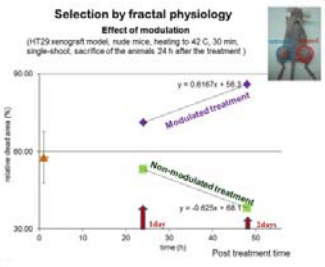












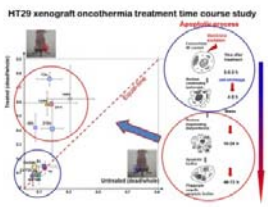
Results

In consequence of the effects multiple changes are recognized in the outer cell-membrane:

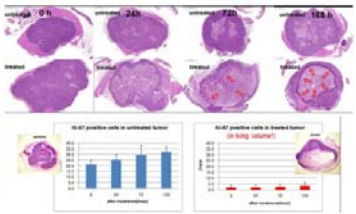
- Inducing apoptotic signal
- Forming membrane-HSP
- Higher transparency
- Higher motility of domains
- Rebinding E-cadherin
- Damages on membrane
- Rectification- demodulation

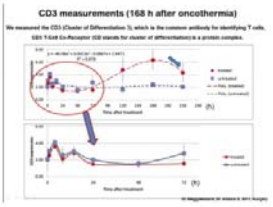
in the cytosol:

- Dilution of the cytoplasm
- Higher pressure developed
- Activated apoptotic pathways
- Activated death receptors
- The effects and their actions in the oncothermia treatment process can be measured in vitro and in vivo as well.



Histomorphological changes, invasion ring





Conclusion

Oncothermia uses cellular nano-effects for targeting and eliminating the malignant cells. It is a feasible and well proven method for natural cell-killing and for immune activation as well.

In memoriam Reka Szasz

References

[1] Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and Practices, Springer, Heidelberg, Dordrecht
[2] Hedden MGV, Cantley LC, Thompson CB (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science 324(5930):1029-1033
[3] Szentgyorgyi A. (1968) Bioelectronics: a study in cellular regulations, defense and cancer, Academic Press, NY
[4] Schwan, H.P: Electrical properties of tissue and cell suspensions. Adv. Biol. Med. Phys. 5, 147-209 (1957)
Schwan, H.P: Determination of biological impedances. In: Physical Techniques in Biological Research, vol. 6, pp 323-406, Academic Press, New York (1963)
Schwan HP (1938) Biophysics of the interaction of electromagnetic energy with cells and membranes. In Grandolfo M, Michaelson SM, Rindi A (eds) Biological Effects and Dosimetry of Nonionizing Radiation. Plenum Press, New York, pp 213-231
Schwan HP (1982) Nonthermal cellular effects of electromagnetic fields: ac-field induced ponderomotoric forces. Br J Cancer 45(5):220-224
[5] Bassingthwaighte JB, Leibovitch LS, West BJ (1994) Fractal Physiology. Oxford Univ. Press, New York, Oxford

P-15: Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Modulation effect in oncothermia

Modulation effect in oncothermia

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]

(1) Department of Biotechnics, St. Istvan University, Budapest, Hungary
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

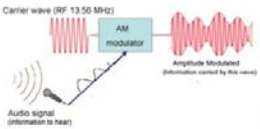
Objective

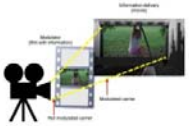
One of the most special and distinguished effect of oncothermia is the modulation. This special effect is important for selection and apoptotic action of oncothermia, applied on basic of multiple patents, [1], [2], [3]. The applied amplitude modulated signal is of course not simple. Presently the amplitude modulated electromagnetic applications have their renewing in the professional literature [Szasz et al Oncothermia, Springer, 2010]. Our objective is to show the oncothermia modulation which is a new way of the modulation technique.

Introduction

The carrier wave (13.56 MHz frequency) delivers the energy focused to the tumor-cells, but the information is delivered by the pattern carrying by the wave. The pattern is formed by the modulation (symmetric change of the amplitude of the carrier). The modulation is similar to the movie-projection. The beam originally starts from a white lamp source, which is the "carrier" of the info. When we see only this, only a white light-spot could be observed, no info is carried. The info is saved on a film, which is illuminated by the source light. The white light started to be "modulated" and the info from the "modulator" started to be carried by the beam. The transparent picture is projected to the silver-screen

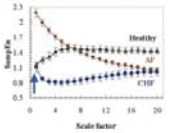
The amplitude modulation in radio-broadcast

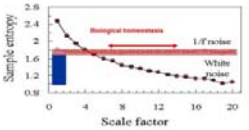




Amplitude modulation like projection (clearly similar to B&W)

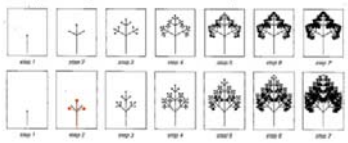
The information which oncothermia has to deliver is the collectivity. This information is characteristic on the healthy cells, they are existing in collective harmony. This harmony makes the full control on their apoptosis, which is the most important prevention against the malignant proliferation. The cellular connections coordinate the harmony, and "glue" the cells together in an integrative tissue, blocking their free movements out. There all are missing in malignancy, where the autonomic cells are able to disseminate by blood-stream and causing the metastases as the main mortality factor in cancer-statistics. The harmonic cooperation of the cells is characterized by the equal entropy in all the scales of the living tissue [Goldberger et.al, 1998]. This is far not the case in any unhealthy conditions, where the homeostatic equilibrium is broken. [Hegyi et.al. 2011] The proper homeostasis in living systems is characterized by the special time-fractal noise so called 1/f frequency. The system which has this noise-harmony, satisfies the constant entropy requirements. [Goldberger et al. 2000]

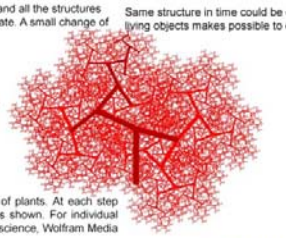




Fractals in space

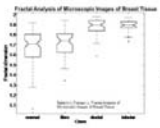
Fractals in nature are widely appearing. The natural shapes of the living organisms, organs and all the structures are fractal0-like organized. The fractals in space are self-similar starting form a simple template. A small change of the template changes the final structure robustly.

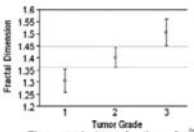


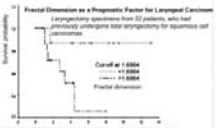


Steps in the evolution of substitution systems that provide simple models for the growth of plants. At each step every growing stem is replaced by a collection of three new stems according to the rules shown. For individual stems this type of branching is known in botany as monopodial. (S. Wolfram: A new kind of science, Wolfram Media Inc. 2002, pp.400)

Space-fractals characterize well main of the pathological statuses.







The problem of the autonomy of the malignant cells makes the treatment very much complicated, because the cancer has its own fractal structure, [Ballerini L Franzen L, Fractal Analysis of Microscopic Images of Breast Tissue].

The analysis of the fractal structures of malignancies could even indicate the stage of the disease [Tambasco M, Magliocco AM, (2008) Relationship between tumor grade and computed architectural complexity in breast cancer specimens, Human Pathology, 39:740-746.].

Careful fractal analysis can make predictive information for the prognosis as well [Delides et al (2005) Fractal Dimension as a Prognostic Factor for Laryngeal Carcinoma. Anticancer Research 25: 2141-2144].

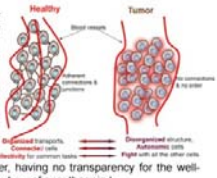
Fractals in time

Same structure in time could be constructed as exists in the space. Analysis of the time-fractals of the dynamism of living objects makes possible to control their wellness as well as to predict their failures.

Method

In oncothermia a special amplitude modulated r by fractal is [2].

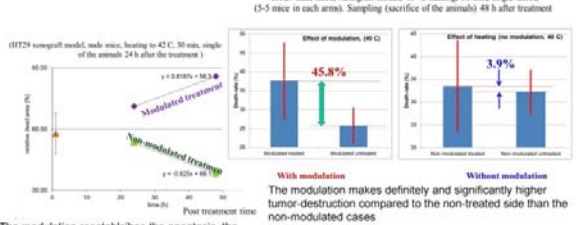
The modulation is far from any sinus or other periodic patterns, it is 1/f spectrum, having definite templates for its construction. The 1/f fluctuation characterizes all the harmonic sounds (like music as well), but of course all the musical pieces are different (even their interpretation could be different) despite of their identical 1/f spectrum. This is which we use for fractal modulation technique. The newest progress applies well established personalized template of the modulation [3], which based on the personal time-fractal of the patient and his own tumor pathology. The modulation electronically needs also special solutions, because the highly capacitive system (and capacitive coupling on impedance basic) could badly modify the spectrum.



The malignant absorption selects according to the disorder of the cancer, having no transparency for the well-chosen modulated RF carrier frequency (It is a patented method and know-how of oncothermia.)

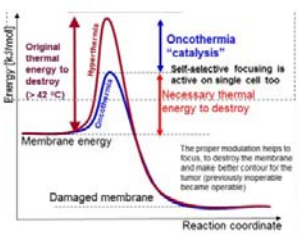
Results

Measurements in comparison the modulated and nonmodulated treatments in vivo show the differences. The modulated treatment side and the untreated side of double tumorous mice shows 45% distortion rate after single-shot (30 min) treatment on 40 C, between the treated and untreated sides of mice (three animals 6 lesions in one measurement point), while the same experimental setup in non-modulated treatment case makes only less than 4% difference between the treated and untreated lesions of the same animals. In study the time-course of the animals, we received also important data: the modulation starts the apoptotic process, and after one and two days the tumor-destructive process is developing, killing the tumor rapidly. In the same experimental setup, the non-modulated treatment makes only the usual destruction after the treatment.



The modulation reestablsihes the apoptosis, the natural cell-killing process, and after 48 h the effect is obviously acting. (HT29 xenograft model on single-tumor-bearing mice.)

The modulation makes definitely and significantly higher tumor-destruction compared to the non-treated side than the non-modulated cases



In memoriam Reka Szasz

Conclusion

Oncothermia modulation is one of the three specialties of this treatment. Its efficacy and its role in the personalization process introduced effective tool for apoptotic cancer-cell destruction.

More detailed explanation and background of the modulation applications in Oncothermia could be obtained from the Oncothermia book [Szasz et al, Springer 2010]. The method is patented

References

[1] Szasz A, Szasz N, Szasz O (2009) Radiofrequency hyperthermia device with target feedback signal modulation. European Patent Application No. EP 080758214
[2] Szasz A, Szasz N, Szasz O (2011) Device and procedure for measuring and examining the signal of systems releasing measurable signals during operation or in response to external excitation. European Patent Application No. EP 057984981
[3] Szasz A, Szasz N, Szasz O (2012) Fractal templates and fractal feedback in homeostatic control. European Patent Application (pending)
[4] Blackman CF (2012) Treating cancer with amplitude-modulated electromagnetic fields: a potential paradigm shift, again?, British Journal of Cancer 106, 241 – 242

P-16: Gabriella Hegyi, Oliver Szasz, Andras Szasz (2012) Synergy of oncothermia and traditional Chinese medicine

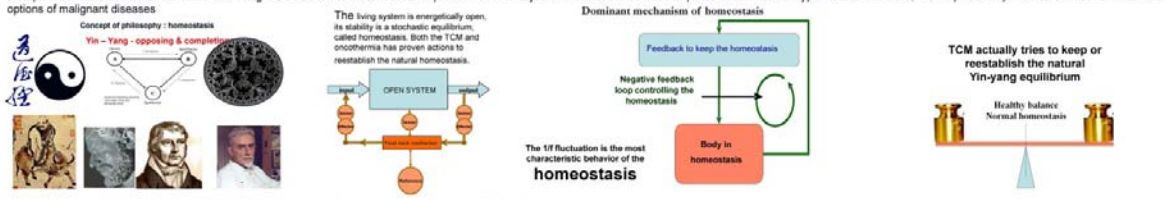
Synergy of oncothermia and traditional Chinese medicine

Gabriella Hegyi[1], Szasz Oliver[2], Andras Szasz[2]

(1) Department of Complementary Medicine, Institute of Forensic Medicine, Medical School, University of Pecs, Pecs, Hungary
(2) Department of Biotechnics, St. Istvan University, Budapest, Hungary

Introduction - Objective

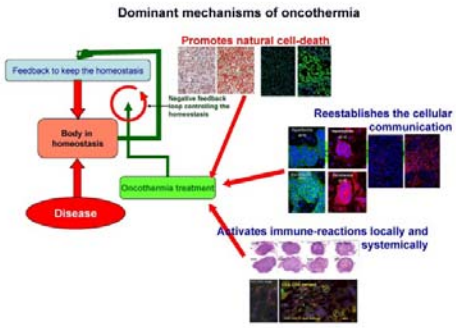
Hyperthermia is the very first oncological treatment [1], started probable on sacral basis. Later Hippocrates described it using physiological process, but surprisingly the other ancient medical approach, the traditional Chinese medicine (TCM, [2]) had not been combined by this method. Probable the philosophical approach was different. Hyperthermia applied constrain force to overheat the body or a part of it, forcing reaction from the system (physiologic changes like blood-perfusion, immune changes, pH or other environmental changes, etc.), and use this anyway unusual reaction for healing. The philosophy of TCM was opposite, not apply any constrains which are out of the normal control, apply only effects to reestablish the normal control, the homeostatic equilibrium. The homeostasis was characterized with a mystic (undefined) chi, which "flows" normally in the homeostasis, and blocked or overstimulated in diseases. Due to the undefined (mainly sacral meaning) categories TCM was not able to be integrated in Western medicine, while heat lost its mystic sacral meaning, and started to be accepted. However this is only the surface of our understanding. In fact the effects of the heating and its consequences remained unclear and so the heat therapy was applied only in home-cares, were categorized as "kitchen" medicine. Nowadays both therapies started to be further examined how integrate these to the modern medical processes. Our objective to show the connection points of the modern hyperthermia and TCM, with especial emphasis on the natural treatment options of malignant diseases

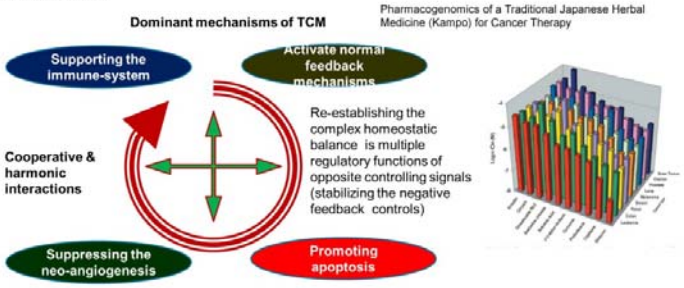


The Western approach to keep or reestablish the homeostasis of the healthy system and the TCM goal to make yin-yang equilibrium are identical in general meaning.

Method

There are various herbal substances in TCM acing palliative or curative on tumorous diseases. These are in increasing interest of western medicine too. For example the pain reduction the "Senecio palmatus". For curative treatments special moxibustion techniques with various complex mixture of herbs could be applied [3]. Synergetic effects of oncothermia [13]. and TCM is expected due to their natural processes. Oncothermia is targeting the tumor cells by intensifying the natural homeostatic loops which is in its goal identical with most of the TCM targets too . [8], [9]. Applying the most modern approaches (of the structure of the living matter, [10], [11], combined with the new physiology ([7], [4], [5], [6]), gives strong point to build up a new synergy between Eastern and Western medicine. [12]

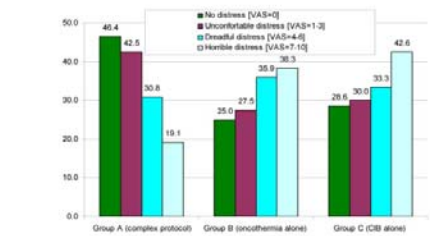


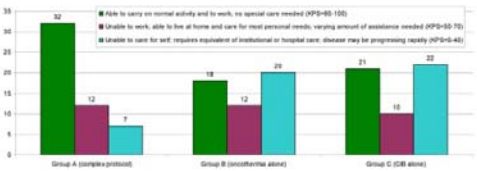


The living homeostasis is complex. Controlling it needs complex approach. Oncothermia is supporting the negative feedback controls of the complex stability. The natural remedies (herbs) are complexly ready for this control too. (this is well shown by the Japanese herbal medicine [13].

Synergy of the methods

[example applications] (Prof.Pang, Clifford Hospital) [14]





Conclusion

Potential of the synergy of high-tech oncothermia and TCM is feasible. Recognition of the distortions in the healthy tissue has some common principles and possibilities of the two methods. The synergy of the ancient knowledge and the high-tech state-of-art of western medical knowledge could be established with this research.

References

[1] Seegenschmiedt MH, Vernon CC (1995) A Historical Perspective on Hyperthermia in Oncology. In: Seegenschmiedt MH, Fessenden P, Vernon CC (eds) (1995) Thermoradiotherapy and thermochemotherapy, Vol 1. Springer Verlag, Berlin, Heidelberg
[2] Unschuld, Paul Ulrich (1985). Medicine in China: A History of Ideas. University of California Press
[3] Longo F. (2007) "Traditional Chinese Medicine in Oncology", in "Proceedings of the 56th S.C.I.V.A.C. National Congress"; June 1/3, 2007 (pp. 230 - 232) Rimini.
[3] Szasz A. Szasz N. Szasz O. (2010) Oncothermia. Principles and Practices, Springer Verlag, Heidelberg, Dordrecht
[4] McMaster university Explores Evidence-based Chinese medicine, http://www.integrativeonc.org/mcmaster-university-explores-evidence-based-chinese-medicine
[5] Jin-Ling Tang, Bao-Yan Liu, Kan-Wen Ma (2008) Traditional Chinese Medicine, The Lancet, 373:1938-1940
[6] Sornette D (2000) Chaos, Fractals, Self-Organization and Disorder: Concepts and Tools. Springer Verlag, Berlin-Los Angeles
[7] Walleczek J (ed) (2000) Self-organized biological dynamics & nonlinear control. Cambridge Univ. Press, Cambridge
[8] Deering W, West BJ (1992) Fractal physiology. IEEE Engineering in Medicine and Biology 11(2):40-46
[9] West BJ (1990) Fractal Physiology and Chaos in Medicine. World Scientific, Singapore, London
[10] Bassingthwaighte, J.B., Leibovitch, L.S., West, B.J. (1994): Fractal Physiology, Oxford Univ. Press, New York, Oxford
[11] Musha, T., Sawada, Y. (eds.) (1994): Physics of the living state. IOS Press, Amsterdam
[12] Longo F. (2007) "Traditional Chinese Medicine in Oncology", in "Proceedings of the 56th S.C.I.V.A.C. National Congress"; June 1/3, 2007 (pp. 230 - 232) Rimini.
[13] Pharmacogenomics of a Traditional Japanese HerbalMedicine (Kampo) for Cancer Therapy; Cancer genomics and proteiomics, 4:81-82 (2007)
[14] Pang C (2011) Randomized three-arm (n=157) prospective clinical trial for rectal cancer patients for synergy of oncothermia with Clifford TCM method.

P-17: Anett Gallne-Valyi (2012) Introduction of the international quality management system: Oncotherm Group

Introduction of the international quality management system: OncoTherm Group

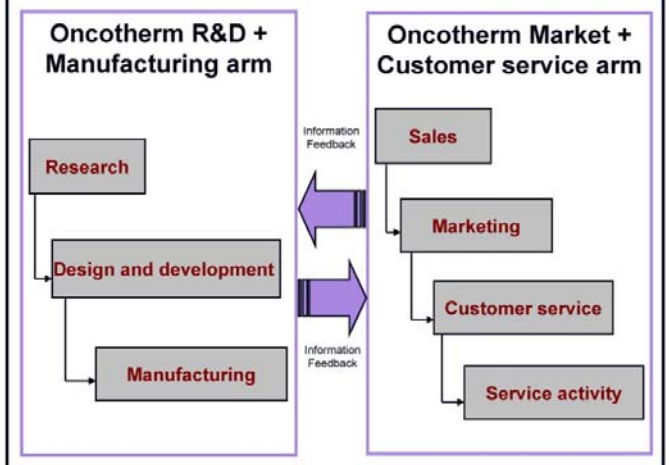
Anett Gállné-Vályi
Quality Manager of Oncotherm Group

OncoTherm Group

Common Quality Management System based on:

- **ISO 9001:2008** Quality Management System. Requirements
- **ISO 13485:2003/AC:2009** Medical Devices. Quality Management Systems. Requirements for regulatory purposes
- **93/42 EEC** Medical Device Directive (MDD)

Therefore we have a common quality system based on the concerning ISO standards and MDD, which provides that our processes are working in a well-controlled way and we advert all requirements/demands coming from our customers and from the national, international regulations.



Approval by TÜV Süd (Munich, Germany)

Oncotherm System (OS) =
Oncotherm Device (OD) + Oncotherm Method (OM)

Made in EU by German approval

Conclusion:

The OncoTherm Group is a marketing method which is in synergy with the devices and jointly presented on the market as a system. There is more than 20 years hard work, experience and knowledge behind the OncoTherm System which certifies that this system has stood the test of the time.

Objectives of the presentation:

- Show the basis of the permanent improvement of the efficacy of oncothermia combined with high quality and complete safety for the users and patients.
- Keeping up the trust of our users and potential customers

Basic points:

- ✓ Oncotherm devices are prepared by team-working of highly qualified experts
- ✓ This unification of the German medical and constructive knowledge with the general European manufacturing culture based on the concerning requirements
- ✓ Oncotherm established a perfect cooperation between the research, medical knowledge, marketing, manufacturing and services
- ✓ Oncotherm operates in the frame of strict common German quality management systems based on the below mentioned aspects:
  - Our devices are distributed for over fifteen countries worldwide, using the German medical knowledge and practical expertise.
  - Most medical feedbacks are coming from the smart German physicians from more than hundred oncothermia installations in the country. This is a good input for the research, design and development as well as an important help of the manufacturing and controlling channels.
  - Feedback from the service activity and the customer service is an integrative part of the company's progress. These pieces of information directly and permanently improve oncothermia method and its devices.
  - Oncotherm manufacturing facilities are organized reacting flexible and quickly on the market demands and challenges.
  - The oncothermia methods are in the focus of our marketing policy. The devices are serving this state-of-art methodology, giving effective weaponry in the hand of the medical staff for fighting in the war against cancer. This marketing strategy requests integrative and tight cooperation with research, design and development amalgamated by interdisciplinary approaches of modern technical and medical knowledge.

Oncothermia marketing and manufacturing arms are working like an integrative unit that makes us strong and effective on the market.

Our quality management systems are satisfying the highest European medical standards. The production process of the devices has ISO13485 medical standard and it is approved by **TÜV Süd Product Service GmbH (Munich, Germany),** who also certifies our products according to the European Medical Device Directive (medical CE-mark).

The business processes have also the highest standard (ISO9001) granted by the **TÜV Süd Management Service GmbH (Munich, Germany),** vouching for the standardized available processes to satisfy oncothermia users and potential customers.

TÜV Süd as the largest Notified Body for medical devices in EU justifies the operation of our quality management systems and keeps it well-controlled to fulfill every necessary European requirements .

TÜV SÜD EN ISO 13485 — CE 0123 — TÜV SÜD ISO 9001

Integrity:

We don't sell only a device but an **OncoTherm System** which consists of **OncoTherm Device** and **OncoTherm Method**.

Full process is controlled by unified overall leadership and unified overall quality system!

SZENT ISTVÁN UNIVERSITY

onco therm

Essence of Oncothermia

Oliver Szasz, Andras Szasz
Department of Biotechnics, St. Istvan University, Budapest, Hungary &
Oncotherm GmbH, Troisdorf, Germany

What are the limits of the old hyperthermia approach?

New paradigm is necessary for oncology

Hyperthermia contradiction:
"The biology is with us while the physics is against us" (J.Overgard)

Oncothermia changes the paradigm:
"The biophysics is with us"

Hyperthermia contradiction:
"The biology and the physics is with us while the physiology is against us" (S.Osinsky)

Oncothermia changes the paradigm:
"The fractal physiology is with us"

Hyperthermia contradiction:
"Reference point is needed!" (J.van der Zee)

Oncothermia changes the paradigm:
"Back to the gold standards, use the energy instead of temperature"

Avoid from high temperature

"Physics is with us, when we use it well"

- Temperature heats up the vicinity of the tumor, it can not be kept locally focused
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.)
- Temperature requests the increase of the safety-cooling on the skin
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely
- Temperature increases the blood-flow in the region, in consequence increases the dissemination
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemopenetration into the tumor (vasocontraction or blood-vessel blockage in the tumor)
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues)
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient

Temperature is not dose

"Physiology is with us"

- ✓ Moderate temperature avoids the natural contra-regulation effects
- ✓ Temperature does not exceed the systemic physiological limit (42 °C)
- ✓ Tumor selection is solved by non-temperature dependent way (electric concept)
- ✓ Focus is to be fixed to the tumor, moves together with the natural body movements (impedance control)
- ✓ Selection is solved on cellular level suppress the dissemination of the malignant cells
- ✓ Cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination
- ✓ Cellular communication (social signal) is reestablished to promote the natural (programmed) cell death for malignant cells
- ✓ Possibility of the cellular molecular exchange (gap junctions) is reestablished to promote the normal function of the cells.
- ✓ The "master switch" (p53 gene) is activated promoting the natural way of various cell killing pathways
- ✓ Cell-membrane permeability is increased to express the HSP on the outer membrane signalizing the cell malignancy for the systemic immune actions.
- ✓ Cell-membrane is excited to ignite various communication pathways in the cells.
- ✓ Electric field blocks the positive feedback loop of tumor-supporting injury currents

Technical specialties of oncothermia

The nano-scale heating

- Target the cell-membrane in nano-scale (correct energy is mandatory)
- Personalized information-delivery is applied (patented)
- Surface cooling is controlled (patented)
- Low voltage large current (at given energy) is applied (patented)
- Time-fractal modulation is applied (patented)
- No temperature measurement is necessary (patented)
- Every parts are designed to the actual task (oncotherm-design)
- Easy to use, comfortable for patient, tailored for patient

Avoid the static approach

"thermostatical considerations are against us"

Measurement of intensive thermodynamical parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)

The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept.

The heat-flow to blood supports the positive feedback loop of the basic-acidic electrolyte balance, and promotes the intensive growth of the tumor by addressed oxygen delivery.

Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead its elimination. (These processes like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.)

Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

Application of dynamic processes

"Thermodynamics and fractal physiology is with us"

- ✓ Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, does not constrain it for false defense.
- ✓ Control of oncothermia is natural, always fitted to the actual conditions (changes of the electrolytes determines its actions).
- ✓ No considerable heat-flow to the blood-stream by oncothermia, no gain of the positive feedback of electrolyte balancing-loop.
- ✓ Thermal gradients make dynamism in a very local area of the cell-membrane of malignant cells. The applied selection focuses on this thermal non-equilibrium.
- ✓ The relatively slow "step-up" heating keeps the non-equilibrium stable for long time for action.
- ✓ The slow heating up does not create considerable physiological contra-actions.
- ✓ The slow heating makes the healthy tissue adapted to the growing temperature.
- ✓ The slow temperature change does not generate high stress and following stress reactions.
- ✓ The applied electric field makes at least three times more effective cell killing than the temperature does.
- ✓ The applied fractal modulation makes possible selecting and supporting the natural processes to activate the natural healing mechanisms and reestablish the healthy "social signal" between the isolated cells, promoting the anti-malignancy collectivity.

Avoid automatisms in treatment guidelines

Guidelines are not "cookery books";
we are in the clinic and not in the kitchen

Everybody is different....

The actual disease is not simple the disease of an organ. This organ belongs to somebody.

The personal differences are modified by the previous treatments and tolerances

The definite similarities after the chemo- or other serious therapies are mainly due to the side effects...

Most of the decisions in serious cases need medical experience, not "only" book-based evidences.

The patients with advanced diseases are not "naïve" in most of the cases. Their high-line treatments need personal decisions, frequently no evidence-based protocols are available for their special cases.

Many times the palliation is necessary, which definitely needs personal decisions.

The psycho-factors are not negligible in the case of malignant diseases.

The personal decision is the responsibility of the experienced doctor...

Make personalized processes

Guidelines of the thinking for experienced physicians

- ✓ Oncothermia is mainly regulated by the patient's tolerance
- ✓ Oncothermia control based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoid burning the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient natural defending/protective system.
- ✓ Oncothermia uses natural processes to cure, understanding and using these needs thinking doctors and their understandings.
- ✓ Oncothermia acts of natural physiology regulation, which needs understanding of the processes.
- ✓ Oncothermia needs permanent dynamic approach, follow-up well what is happening during the treatment.
- ✓ Step-up heating is the basic treatment approach, which requests permanent care on the process.
- ✓ The effect of the activated natural processes are not acting immediately. To have a control treatment-by-treatment is essential.
- ✓ The patient's well being during and after the treatment is necessary side of the well conducted protocol.
- ✓ Complete relaxation could be supported by relaxing music, video or sound effects during the treatment.

In memoriam Reka Szasz

Production support by LabView-based data-acquisition systems

Skrihár Gábor
Development engineer, Oncotherm Group

The necessity of integrated data-acquisition systems

During the production of a product a lot of tests and measurements are done. First the electronic boards are checked separately, then the modules which are built from them are tested separately, and finally a lot of tests are conducted on the assembled system. During these test a lot of data is acquired from the product, but – especially at the final testing of the product – the data acquisition could be difficult, because, because:

- The testing time is so long, that the continuous observation of the test is not possible
- If during the measurement more instruments are used, the simultaneous and continuous observation all of them is not possible.
- A lot of instruments don't provide built-in data acquisition and storing
- Although some instruments have this function, it could be difficult to synchronize the data acquired by various instruments.

The solution of these problems is such a data collection system, that in real-time collects and synchronizes all of the information, that the used instruments provide during the measurement and then stores them into a common database, allowing the common processing of them. By this way the efficiency of the production could be greatly increased. For us at Oncotherm is a priority to increase both the speed and the quality of the production of our products, so we started to develop integrated data-acquisition systems to support our production tasks.

The main element of these systems is the LabView program suite, which is developed especially for data-acquisition and instrument control and is provided by National Instruments. The main task of LabView is to control the NI's own DA units, but the products of the most important instrument manufacturers are controllable by the suite too. During our projects we use both NI instruments and the instruments of other manufacturers (Tektronix, Rhode&Schwartz) too.

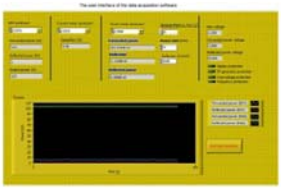
The instrumentation of a test treatment

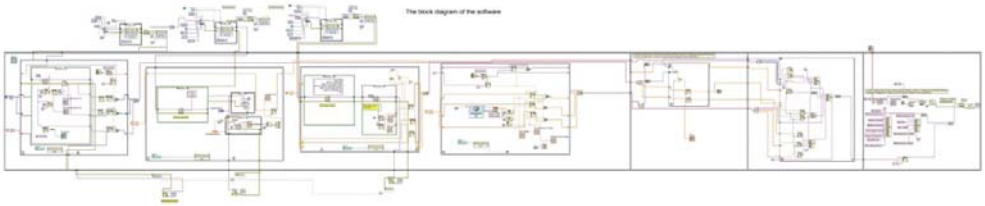
One of our main ambitions is the monitoring of the manufactured EHY-2000 oncothermia devices during their final tests, which means lots of test treatments continuously day and night. During these test treatments important data can be collected about the general behavior and the reliability of the system, which are the key factors of the quality of the product.

The device sends important information about its state by RS232 serial port and the inner signal lines of the device are monitored by NI data-acquisition devices.
A typical data acquisition system consists of the following instruments and provides us the following information:

- EHY-2000:
  - By serial port: time after the start of the treatment, output power, reflected power and the states of the various protection signal lines
  - By direct monitoring of signal lines: the control voltage of the amplifier and the voltages proportional with the forwarded and reflected power.
- R&S RF power meter: used as an external reference for the accuracy of the power measurement of the device.
- Multimeter: used as a current meter to monitor the correct consumption of the amplifier.

By using the data provided by the reviewed instrumentation we can get a clear picture about the energetic efficiency and the general behavior of the amplifier, which – as the most difficult part of the device – needs the most testing.





One part of the recorded data file

Forwarded power [dW]	Reflected power [dW]	Display protection	Amplifier protection	Overvoltage protection	Frequency protection	Cpu protection	Forwarded power [dBm]	Reflection-loss [dBm]	Reflected power [dBm]	Mains voltage [V]	Forwarded power voltage	Reflected power voltage
199	1	not active	not active	not active	not active	4.94	343,203	1,194	1,199	3,211	2,799	-0,052
199	1	not active	not active	not active	not active	4.94	343,203	1,194	1,199	3,211	2,797	0
199	1	not active	not active	not active	not active	4.94	343,203	1,194	1,199	3,206	2,793	-0,01
199	1	not active	not active	not active	not active	4.94	343,203	1,207	1,251	3,206	2,775	-0,052
199	1	not active	not active	not active	not active	4.94	343,077	1,204	1,177	3,211	2,75	-0,057
197	1	not active	not active	not active	not active	4.94	343,203	1,205	1,251	3,206	2,755	-0,052
196	1	not active	not active	not active	not active	4.94	343,265	1,207	1,248	3,205	2,753	-0,052
195	1	not active	not active	not active	not active	4.94	343,203	1,207	1,242	3,211	2,75	0
194	1	not active	not active	not active	not active	4.94	343,265	1,207	1,245	3,248	2,75	-0,065
194	1	not active	not active	not active	not active	4.94	343,178	1,207	1,248	3,253	2,756	-0,067
193	1	not active	not active	not active	not active	4.94	343,203	1,207	1,245	3,24	2,753	-0,065
193	1	not active	not active	not active	not active	4.94	343,134	1,207	1,245	3,229	2,737	-0,065
194	1	not active	not active	not active	not active	4.94	343,228	1,207	1,248	3,218	2,734	-0,065
194	1	not active	not active	not active	not active	4.94	343,121	1,208	1,248	3,206	2,737	0
194	1	not active	not active	not active	not active	4.94	343,11	1,208	0	3,206	2,737	-0,062
197	1	not active	not active	not active	not active	4.93	343,084	1,208	1,251	3,205	2,733	-0,052
199	1	not active	not active	not active	not active	4.94	343,057	1,209	1,228	3,218	2,745	-0,013
199	1	not active	not active	not active	not active	4.93	343,203	1,208	1,276	3,195	2,727	0
199	1	not active	not active	not active	not active	4.94	343,058	1,207	1,232	3,172	2,693	-0,065
199	1	not active	not active	not active	not active	4.94	343,013	1,209	1,224	3,195	2,699	-0,013

Other possible usages

Of course, the data-collecting systems always follow the demands of the current projects, capitalizing the flexibility of the LabView-based DA systems. On the grounds of our experiences until now we have more ways of improvement on this field. The most important ones are:

- Research support: integrated data acquisition during laboratory experiments, focusing to collect data from the Lab-EHY laboratory device and the 4-channel thermometer also developed by Oncotherm.
- Production support: automated testing of our products by LabView-based instrumentations

Realizing sing these conceptions we can improve both improve the quality of our products and the affectivity and the speed of our R&D projects, so we are committed towards these ways.

P-20: Gyula P Szigeti, Gabriella Hegyi, Oliver Szasz (2012) Hyperthermia versus Oncothermia: cellular effects in cancer therapy

Hyperthermia versus Oncothermia: Cellular effects in cancer therapy

Gyula P Szigeti*, Gabriella Hegyi**, Olivér Szász

Department of Biotechnics, St. Istvan University, Godollő, Hungary
**Department of Physiology, University of Debrecen, Hungary and Institute of Human Physiology and Clinical Experimental Research, Semmelweis University, Hungary*
***Department of Complementary and Alternative Medicine, University of Pécs, Hungary*

ABSTRACT

Hyperthermia means overheating of the living object completely or partly. Hyperthermia, the procedure of raising the temperature of a part of or the whole body above normal for a defined period of time, is applied alone or as an adjunctive with various established cancer treatment modalities such as radiotherapy and chemotherapy. 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 force and 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.

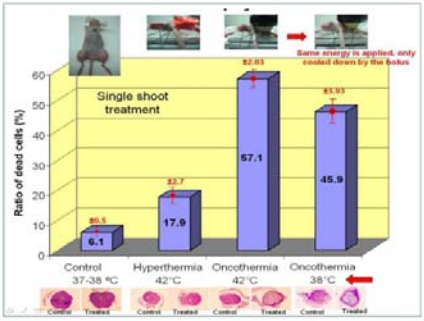


Figure 1.
The cell-destruction ability of oncothermia is three-times higher than hyperthermia at the same 42°C temperature. Pumping the same energy as for temperature 42°C, but cooling the lesion by outside water-bolus (to 38°C temperature), the efficacy of the cell-destruction remained much higher in oncothermia than in hyperthermia at 42°C temperature.

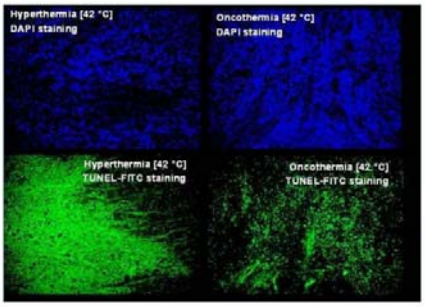


Figure 2.
Upper panel: DAPI staining (stains the double strains of DNA only), lower panel TUNEL-FITC staining (enzymatic label of the strain-break of the DNA).

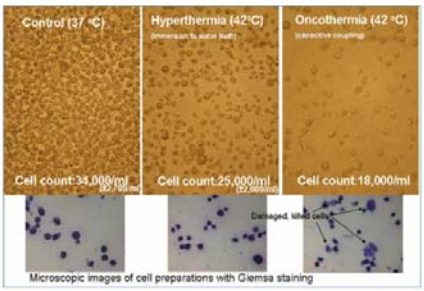


Figure 3.
Comparison of cell death induced by oncothermia with traditional hyperthermia (*in vitro* experiments with fixed sample): HL-60 leukaemia cell line.

ACKNOWLEDGEMENT

Authors acknowledge the experimental work and fruitful discussions of Dr. Nora Meggyeshazi and Dr. Gabor Andocs.

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.

Mechanisms induced by hyperthermia:

- *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.*
  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.
- *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. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases.
- *Cellular and intracellular mechanisms of thermal effects in the hyperthermia - Cell metabolism: hypoxia, pH, ATP and its consequences*
  Summarising 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 sensitise tumour cells to hyperthermia in the sense of a positive feedback mechanism. Relevant pathogenetic 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 β-hydroxybutyric acid,
  4. an increase in CO_2 partial pressures,
  5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
  6. an inhibition of the Na^+/H^+ antiporter in the cell membrane.

  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^+ 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.
- *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.

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. 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.

Mechanisms induced by oncothermia

- *Oncothermia promotes the programmed cell-deaths of tumor*
  Detecting the double strains of DNA (DAPI staining, see *Figure 2.* upper panel) and measuring the enzymatic labeled strain-breaks of DNA (TUNEL-FICT, see *Figure 2.* lower panel) the apoptosis is highly likely in oncothermia. 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.
- *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, see *Figure 3.* 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.

P-21: Gabor Andocs, Nora Meggyeshazi, Y. Okamoto, Lajos Balogh, Oliver Szasz (2012) Bystander effect of Oncothermia

Bystander effect of Oncothermia

Andocs, G.[1], Meggyeshazi, N.[2], Okamoto, Y.[1], Balogh, L.[3], Szasz, O.[4]

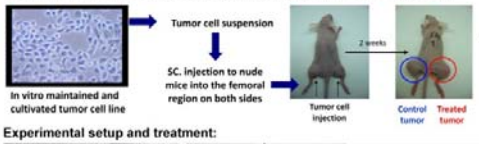
(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(2) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
(3) „Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary
(4) Biotechnics Department, Faculty of Engineering, St. István University, Budapest, Hungary

Introduction

Oncothermia (OTM) is an electro-hyperthermia modality, a long time (since 1989) applied method in oncology,[1] with great clinical success [2]. OTM changes the paradigm of hyperthermia by targeted microscopic heat-liberation at the membrane of the malignant cells. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The tumor destruction efficacy and the role of temperature independent effects of the OTM was proven earlier by laboratory research, and presented elsewhere [3],[4].
Bystander effect (abscopal effect) means that a local tumor treatment can affect the behavior of the far distant metastases. It was first discovered by radio-oncologists and remained higly controversial topic until recent years. [5],[6]. Intensive research is conducting to reveal the immunbiological basis [7],[8],[9] and mechanism of action of this effect [10] and using the benefits in the regular oncological practice. Objective is showing the newest results of oncothermia in research bystander effect.

Methods

Animal model:
HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mouse.

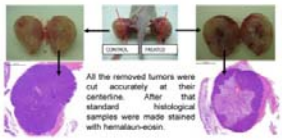


Experimental setup and treatment:

A single shot 30 min oncothermia treatment was done, reaching maximum 41-42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense m3300).

Study design:
Time course study was performed. After a single shot treatment, sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 hours. 3 mice were sacrificed at each time point, keeping 5 sham treated animals.

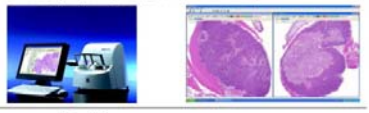
Tumor sample processing I.:
24 h later the single-treatment animals were sacrificed and both the control and treated tumors were removed and studied in pairs.



Tumor sample processing II.:
Due to the extremely high number of the tumor samples, tissue microarray (TMA) technology was used to perform accurate immono-histochemical reactions on many samples in one block.

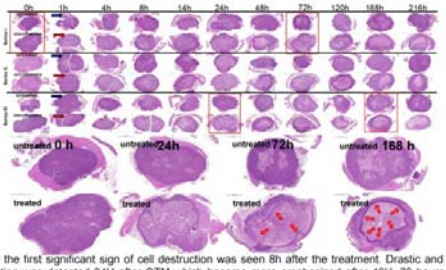
Immunohistochemistry (IHCH):
The following reactions and IHCH analysis were performed on the TMA samples: TUNEL (Invitrogen); TRAIL (DR5), HSP70 (Cell Signaling); Myeloperoxidase (Sigma); CD3 (Dako), CD4 (ABDSerotech).

Digital microscopy analysis:
All histological slides were digitalized using Panoramic Slide Scanner (3D HisTech) and special software was used for imaging and evaluation.



Results

1. Histomorphological changes:



Morfologically the first significant sign of cell destruction was seen 8h after the treatment. Drastic and selective tumor-destruction was detected 24H after OTM which became more emphasized after 48H. 72 hours after the treatment a significant leucocyte infiltration (marked with red arrows) appeared around the destructed tumor tissue and reached its maximum 168 hours after the treatment.

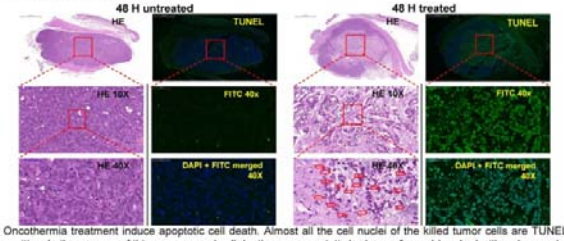
References:
(1) Szasz A. (2007) **Hyperthermia, a modality in the wings.** J Cancer Res Ther. 3:56-60.
(2) Szasz A, Szasz O. (2010) **Oncothermia. Principles and Practices.** Springer Verlag. (http://www.springer.com/biomed/cancer/book/978-90-481-9497-1 Schungermeier) Heidelberg, Dordrecht
(3) Andocs G, Szasz O, Szasz A. (2009) **Oncothermia treatment of cancer: from the laboratory to clinic.** Electromagn Biol Med. 28(2):148-60.
(4) Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A. (2009) **Strong synergy of heat and modulated electromagnetic field in tumor cell killing.** Strahlenther Onkol. Feb;185(2):120-6.
(5) Silva C, Formenti, Sandra Demaria. **Systemic effects of local radiotherapy.** Lancet Oncol 2009; 10: 718–26
(6) William F. Morgan, Marianne B. Sowa, **Non-targeted bystander effects induced by ionizing radiation.** Mutation Research 616 (2007) 159–164
(7) Robert FA Wallin, Andreas Lundqvist,Solveig H. Moré, Arne von Bonin, Rolf Kiessling,Hans-Gustaf Ljunggren, **Heat-shock proteins as activators of the innate immune system.** TRENDS in Immunology Vol.23 No.3 March 2002
(8) Stephan R. SCHOTTA, Heike NAVE, Pirouzeh KOMANDI, Kerstin SCHÜTZ, Reinhard PABST, Elisabeth M. JAFFEE, **Apoptotic but not necrotic tumor cell vaccines induce a potent immune response in vivo.** Int. J. Cancer: 103, 205–211 (2003)
(9) Oliver Kepp, Antoine Tesniere, Frederic Schlemmee,Mickael Michaud, Laura Senovilla,Laurence Zitvogel, Guido Kroemer, **Immunogenic cell death modalities and their impact on cancer treatment.** Apoptosis (2009) 14:364–375
(10) Akhilesh D. Garg, Dominika Nowis, Jakub Golab, Peter Vandenabeele, Dmitri V. Krysko, Patrizia Agostinis, **Immunogenic cell death, DAMPs and anticancer therapeutics: An emerging amalgamation.** Biochimica et Biophysica Acta 1805 (2010) 53–71

(pandocs@gmail.com)

In memoriam Reka Szasz

2. Hallmarks of immunogenic cancer cell death

2.1 Apoptotic body formation

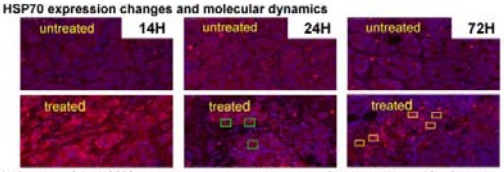


Oncothermia treatment induce apoptotic cell death. Almost all the cell nuclei of the killed tumor cells are TUNEL positive. In the process of this programmed cell death many apoptotic body was formed (marked with red arrows).

2.2. TRAIL (DR5) expression

TRAIL (DR5) is a higly immunogenic cell surface receptor. Expression was increased in the treated side 8H after the treatment and became more emphasized after 14H.

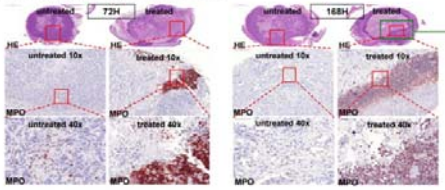
2.3 HSP70 expression changes and molecular dynamics



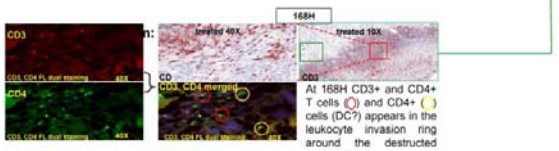
Definite increase of the HSP70 expression was observed 14 hours after the treatment. After 24 hours, unusual molecular dynamic changes of the increased amount of HSP70 can be visible: intracellular condensation ( ) and relocalization to cell membrane. After 72 hours the membrane relocalization of the HSP70 became more emphasized, especially in the region of the leukocyte invasion. ( )

3. Strong local immune reaction

3.1 Myeloperoxidase (MPO) detection:



The leukocyte invasion ring what appears at 72H and became very characteristic at 168H around the destructed tumor area, contains high number of MPO positve cells (neutrophiles, macrophages)



At 168H CD3+ and CD4+ T cells ( ) and CD4+ ( ) cells (DC?) appears in the leukocyte invasion ring around the destructed tumor tissue.

Conclusions

1. **Oncothermia can induce programmed cell death which create many apoptotic bodies**
2. **Oncothermia induced cell death is higly immunogenic, showing all the key molecular pattern dynamic changes what is characteristic of immunogenic tumor cell death**
3. **Oncothermia treatment can induce strong and very unusual immun reaction at the site of the treatment**
4. **The local antitumor immune reaction can be systemic, if the host has an intact immune system, and this process can control the distant metastases by bystander effect, making possible the systemic control of the malignant disease with local treatment.**

(The intensive research is in progress on immunocompetent models!)

Acknowledgement:

TATEYAMA KAGAKU GROUP

oncotherm highTech medicine

P-22: Yun Hwan Kim, Woong Ju, Cheol Kim (2012) Electro-hyperthermia for refractory ovarian cancer patient having bone marrowdepletion as a consequence of long-term chemotherapy: Case report

Electro-hyperthermia for refractory ovarian cancer patient having bone marrow depletion as a consequence of long-term chemotherapy
: Case Report

Yun Hwan KIM, Woong JU, Seung Cheol KIM
Department of Obstetrics and Gynecology,
Ewha Womans University Mokdong Hospital, Seoul, Republic of Korea

Abstract

Modulated electro-hyperthermia is an emerging complementary treatment option for refractory solid tumor. Early experience suggests that it may have advantages over conventional hyperthermia with exceeding efficacy, and less complication. Herein, we describe a case of platinum-resistant, refractory ovarian cancer successfully controlled by the combination of electro-hyperthermia and dose-dense chemotherapy. On the way of repeated treatment for advanced or relapsed ovarian cancer, we finally encountered uncontrollable tumor growth simultaneously with multi-drug resistance and bone-marrow depletion. In this case, we observed stable disease over long time (1 year <) without any significant hematologic complications by applying electro-hyperthermia and weekly single chemo-agent. The gross lesion was disappeared on CT scan and PET imaging with the decline of serum CA-125 marker. Electro-hyperthermia combined with dose-dense chemotherapy could be a good treatment option for the selected, refractory ovarian cancer patients without significant hematologic complications.

Case

Refractory ovarian cancer patient aged 62 was transferred at May 2011.

2010.1.20 Debulking operation (Epithelial Ovarian cancer, Stage IIIc)

2010.1-2010.9 Paclitaxel-Carboplatin #9 ➔ Complete Remission

2011.1.4 Recurrence (liver metastasis was detected by PET)

2011.1-2011.7 Belotecan-Cisplatin # 6 ➔ Partial Remission but suffered from severe bone marrow depletion

2011.7 Transferred for electro-hyperthermia (Oncothermia) treatment

2011.8~2012.2.20 Weekly Cisplatin #4 + Oncothermia (x3/week) ➔ Partial remission without hematologic complications

2012.3 Regimen changed to Weekly Paclitaxel + Oncothermia due to elevation of tumor marker ➔ Stable disease

Images & Tumor marker (CA 125)

Figure 1. CT scan follow-up.

Liver metastasis was disapeared after dose-dense chemotherapy and concomitant oncothermia

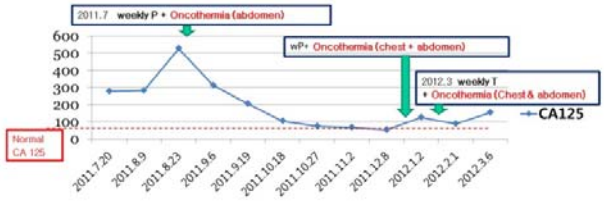


Figure 2. serum CA125 follow-up.

Serum level had declined after dose-dense chemotherapy and concomitant oncothermia

P-23: Doo Yun Lee, Hyo Chae Paik, Seok Jin Haam (2012) Hyperthermia in the patients with small cell lung cancer

Hyperthermia in the patients with small cell lung cancer

Doo Yun Lee, Hyo Chae Paik, Seok Jin Haam
Department of Thoracic & Cardiovascular Surgery,
Gangnam Severance Hospital, Yonsei University College of Medicine,
Seoul, Republic of Korea

Introduction

Small cell lung cancer (SCLC) has more rapid doubling time and earlier development of widespread metastasis than non-small cell lung cancer. SCLC is highly sensitive to initial chemotherapy (CTx) and radiotherapy (RTx) but, recurs or spreads quickly. In addition, the surgical role in SCLC is still insignificant. So, the new treatment modality besides conventional treatments is needed to get a better prognosis. The aim of this study is to evaluate the effectiveness of hyperthermia in SCLC patients

Materials and methods

We retrospectively reviewed the medical records of 28 SCLC patients who were diagnosed with SCLC from January 2004 to December 2012. Nineteen patients underwent the treatment of hyperthermia (hyperthermia group), and 9 patients did not undergo (control group). The patients who underwent < 1 cycle of hyperthermia or surgical procedures were excluded. For hyperthermia, EHY-2000 system (Oncotherm GmbH, Troisdorf, Germany). One cycle was defined as 12 times (1 hour per time, 2 times per week). The patients' characteristics and survival rates of each group were analyzed.

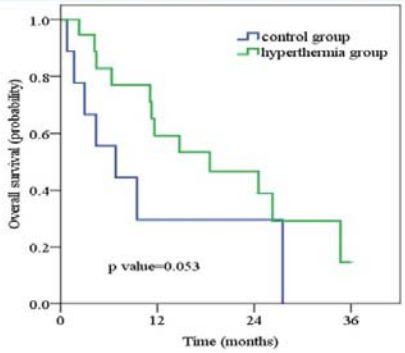
Results

Patients' characteristics

	Hyperthermia group	Control group	P value
Gender			0.615
Male	16	8	
Female	3	1	
Median age (range, years)	67 (52~79)	67 (58~84)	0.148
Concurrent treatments			
CTx	14	6	0.516
RTx	8	0	0.024
Median follow-up time (range, months)	14.7 (2.3~36.0)	6.8 (0.8~27.5)	0.442

The Gender distribution, median age, and median follow-up time were not statistically significant. The numbers of patients who underwent concurrent CTx were not different in each group but, more patients in hyperthermic group underwent concurrent RTx than control group

Overall survival rates



Comparing overall survival rates between hyperthermia group and control group, the survival rate of hyperthermia group was better than that of control group, but it did not have statistic significant (p value=0.053).

Discussions

Hyperthermia in SCLC has a lot of important advantages. 1) It is applicable to patients with poor functional status. 2) It can be performed with CTx and RTx. 3) It has very low morbidity. But, there are several limitations in this study. 1) Small number of patients was included. 2) There are bias of CTx and RTx.

Although the results of this study did not reach the statistic importance, hyperthermia may be good treatment option in the patients with SCLC.

P-24: Vakalis Ioannis, Kouridakis Petros, Daniilidis Lazaros, Natsouki Valentina, Kalyvas Spyros, Maragkos Michail, Dimitriadis Konstantinos (2012) Loco regional hyperthermia in Greece: A new treatment modality for treating deep seated tumors. Two years clinical experience from Thessaloniki hyperthermia's – Oncology operation center – New challenges

"LOCO REGIONAL HYPERTHERMIA IN GREECE: A NEW TREATMENT MODALITY FOR TREATING DEEP SEATED TUMORS. TWO YEARS CLINICAL EXPERIENCE FROM THESSALONIKI HYPERTHERMIA'S - ONCOLOGY OPERATION CENTER-NEW CHALLENGES"

ONCOHYPERTHERMIA OPERATION CENTER
TSIMISKI 82,THESSALONIKI HELLAS

VAKALIS IOANNIS(1),KOURIDAKIS PETROS(2),DANIILIDIS LAZAROS(3),NATSOUKI VALENTINA(4),KALYVAS SPYROS(5),MARAGKOS MICHAIL(6),DIMITRIADIS KONSTANTINOS(7).

1.Surgeon.Department of surgery 424 General Army Hospital, Sub-director
2.Surgeon.Department of surgery 424 General Army Hospital, Director
3.Surgeon MD,MH,PhD
4.Dermatologist
5.General Practitioner
6.Radiotherapist-Oncologist.Department of oncology 424 General Army Hospital,MBA,Director.
7.Medical Oncologist. Department of Oncology,Theagenio cancer institute,Ex-Director.

We treated 75 patients with cancer between August 2010 and September 2012.We used the "OncoTherm 2000plus system (13,56 Mhz) medical device in our hyperthermia operation center.

REPORTING RESULTS

1.CENTRAL NERVOUS SYSTEM TUMORS

-3 Men with gliomas and 1 man with astrocytoma.We noticed general improvement as regarding to their performance status and reduction of their tumor mass in routine radiologic tests.

2.HEAD AND NECK-ORAL CAVITY

-1 Man suffering of tongue cancer who received 12 trials of local deep-heat (HT) treatment having received chemo-radiotherapy before. This man developed progressive disease with lung metastases in the end of the treatment.

-1 Man with epithelial (squamus cell-SCC) carcinoma who has been treated with HT together with Radiotherapy. His tumor has been reduced during therapy on the order of 90%.One year later this patient died having stopped any other therapy.

3.LUNG CANCER

-9 cases,3 Women-6 Men

-1 Woman having tumor at the right lower lobe. After 24 trials her tumor almost completely disappeared (no evidence of primary tumor).

-1 Woman having cancer at the left lower lobe after surgery and chemotherapy with x-knife. Her tumor has been reduced on the order of 40%.

-1 Woman having cancer at the right upper lobe. Her cancer has been partially responded to treatment and she is programmed to be operated.

-4 Men having medically inoperable pulmonary disease remained with no response to treatment

-1 Man having medically inoperable pulmonary disease paused treatment after his 3rd trial.

4.BREAST CANCER

-16 women having breast cancer,4 with early stage (stages II-III) and 14 with locally advanced and /or tumor recurrent disease (stage IV).

-Women from the first group received 12 trials HT and 3 of them are currently under careful medical supervision. The last one having cancer in both of her breast paused treatment during her 3rd trial.

- Amongst the women from the second group :

-1 of them having receiving 12 trials HT together with chemotherapy her tumor completely responded to treatment and demonstrates no evidence of primary tumor according to her MRI test.

-7 of them with liver metastases demonstrated stabilized response according to their radiologic exams.

-1 of them with liver metastases having receiving chemotherapy sessions ,she finally developed tumor necrosis syndrome and died.

-2 of them having pulmonary metastases, the one with no response to treatment and the other with minor reduction to her tumor size according to their x-ray tests.

5.STOMACH CANCER

-1 Man having stomach cancer after surgery having one meta lesion in his liver. After 12 trials performed partial response of his metastasis.

-1 Woman having medically inoperable stomach cancer 88 years old paused treatment after 1st session.

6.GIST

-1 Woman having GIST cancer 77 years old. After 12 trials she did not responded to treatment and she died 3 months later of anorexia nervosa.

7.LIVER CANCER

-1 Man having liver cancer and hepatitis-C having two main tumor lesion in his liver, one 12cm and the other 1cm over his left adrenal gland. He has had liver chemoembolization with about 60 trials. His first tumor lesion shrinked on the order of 50-60% while the other did not responded to treatment at all.

8.GALLBLADDER CANCER

-2 Men and I woman having cholangiocarcinoma.Amongst then 1 man and 1 woman having liver meta-lesions have been undergone cholocystectomy and adjuvant systematic chemotherapy (12 trials) did not responded well to therapy.

-1 Man having medically inoperable cholangiocarcinoma died after the 4th trial.

9.PANCREATIC CANCER

-Among 10 medically inoperable patients having pancreatic cancer,7 men and 3 women.

-2 of the men received over 30 trials HT together with adjuvant chemotherapy and they demonstrated partial response to therapy and they live up to now (2 years later) with good quality of life.

-1 Man died after 12 trials HT

-1 Man having metastases lesions in his liver and in the lungs from the beginning , died of intrabronchial hemorrhage.

-3 Men paused HT after 4-5 trials.

-1 Woman suffering of medically inoperable pancreatic cancer after 36 trials of adjuvant chemotherapy together with HT trials demonstrated a good performance status,her quality of life improved and 1.5 year later she died of acute renal failure.

-1 Woman suffering of inoperable pancreatic cancer paused therapy after 7 trials HT.

-1 Woman having medically inoperable pancreatic cancer with 27 trials HT and adjuvant chemotherapy despite the fact that her meta lesions in her liver and her tumor markers have been increased, performs up to now (about 13 months) an excellent quality of life.

10.COLON CANCER

-Among 8 incidences with colon cancer,5 men and 3 women developed meta lesions in their liver:

-1 Man with a single liver metastasis after ablation and 12 trials HT this metastatic lesion completely disappeared.

-1 Man received 12 trials.(We have no more data)

-3 Men paused trials in the middle of their treatment.

-1 Woman with meta lesion in the liver and in the lungs having received 12 double trials,she demonstrated improvement in her lung tumors according to her radiological exams during her follow-up.

-1 Woman with multi meta lesions in liver,ovaries,uterus paused treatment during the 3rd trial suffering of acute peritonitis and and acute abdomen.

-1 Woman suffering of tumor relapses in her abdomen paused treatment during 4th trial.

11.RENAL TUMORS-GRAWITZ

-1 Man with right Grawitz tumor 79 years old, with meta lesions in his lungs had 3 double trials. He paused treatment and some time later he died of acute respiratory inadequacy.

12.OVARIAN CANCER

-14 patients with ovarian cancer.

-Amongst them:

-13 received adjuvant chemotherapy.

-3 having undergone some trials HT, paused treatment.

-4 having liver metastases, demonstrated improvement in quality of life after 12 trials.

-3 having multiple metastases demonstrated progressive disease after 12 trials.

-1 Woman with tumor reccurence after 24 trials These died of allergic reaction to chemotherapy.

-1 Woman developed ascites after 24 trials and died of peritonitis and acute abdomen .

-1 Woman received 24 trials without chemotherapy performed complete remission to meta lesions.

-1 Woman stage IV after total hysterectomy with liver meta lesions,ascites and chemoprophylaxis with tamoxifen having received 139 trials HT.After therapy performed shrinkage of tumor lesions and a reduction to tumor markers levels showing evidences of a low density lesion with central necrosis in her previous tumor lesion according to her radiological findings .

13.ANUS CANCER

-1 Man and 2 women with anus cancer.

-1 Man with remission around the tumor bed after surgery having a meta lesion in the left upper lobe. He received 12 trials of HT with adjuvant chemo-radiotherapy. He demonstrated partial remission to therapy according to radiological images. He finally died of brain attack.

-1 Woman with anus cancer who did not want to be operated. She received chemotherapy and during her second trial she died of undiagnosed meta lesion in the brain.

-1 Woman paused after 1st trial.

14.SARCOMA

-2 women with sarcoma both paused treatment during trials the first one during 4th and the second during 5th trial.

CONCLUSIONS:

1.Hyperthermia combined with chemotherapy and/or Radiotherapy demonstrates significant clinical response rates as compared to chemotherapy and/or Radiotherapy alone in some cases.

2.Hyperthermia is quite well tolerated and does not significantly increases the toxicity of Radiation or combined modality therapy.

3.In contrast, estimation of the severity of late effects is often haphazard and incomplete depending on the sensitivity of the test used for detection. Over time treatment change frequently, making it difficult to evaluate the role of each component to the outcome. Indications show that life expectancy from the statistical point of view with the addition of hyperthermia may be improved. Hence:

3.More protocols is needed to be currently designed based on clinical experience randomizing chemo radiation therapy alone versus hyperthermia together with chemo/radiotherapy so that the role of hyperthermia in the neoadjuvant treatment of cancer may be better defined.

PI-01: Janina Leckler (2012) Oncotherm Group Marketing & Sales Strategy

Oncotherm Group
Marketing & Sales Strategy

Janina Leckler, Marketing & Sales Manager, Oncotherm Group Germany/Hungary

SALES ORGANISATION

Organisation and coordination/support:

Oncotherm GmbH, Germany

Freelancer in Germany:

The Pockwood Corporation

International Distributors and their territories:

C-Therm Africa
South Africa, Angola, Botswana, Democratic Republic of the Congo, Ghana, Ivory Coast, Kenya, Namibia, Nigeria, Rwanda, Tanzania, Zambia, Zimbabwe, Angola

Ertesad Limited
Cyprus, Armenia, Azerbaijan, Belarus, Kazakhstan, Russia, Turkmenistan, Ukraine, Usbekistan

Hospi Co. Ltd.
South Korea, Australia

Instituto Di Medicini Biológica
Brazil

Oncocure Inc.
Canada, Belize, Costa Rica, El Salvador, Guatemala, Honduras, India, Mexico, Nicaragua, Panama

Tamer Corporation for Medical Supplies
Jordan, Iraq, Kuwait, Lebanon, Qatar, Saudi Arabia, United Arab Emirates

Tateyama Co. Ltd. (Thailand) / Tateyama Machine Ltd.
Japan, Thailand, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Singapore, Vietnam

TEK Grup Saglik Hizmetleri A.S.
Turkey, Cyprus (Turkish part)

The Pockwood Corporation
Belgium, Netherlands

Marketing Organisation

Head: Oncotherm GmbH, Germany

Assistance: Oncotherm Kft., Hungary

Marketing actions for the support of sales and customer satisfaction:

Monthly Newsletter with information on events, new developments and the science

Brochures about devices and the method for doctors, special patient brochures

Oncothermia Journal (published three times a year)

Website with special login-area for customers

Films about treatment and device use

Yearly Oncotherm Symposium

Oncotherm booth at national and international conferences and events

Publications (Oncotherm-books and many scientific articles)

Press Releases

Oncotherm Products Overview

Mr. Balázs Ács Executive Manager, Oncotherm Ltd.

Main products:

Booster

This product is new kind of innovations in the field of complementary cancer treatment. Its use enhances the effects chemo- and/or radiotherapies, as well as well applicable for drug-targeting and personalization of any other medications, irrespective its i.v, oral, injection or other introduction.

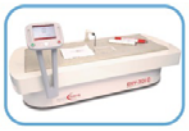
EHY-1020 IL

The EHY-1020 IL is a device specialized of intraluminar application mainly for tumorous diseases of prostate irrespective its malignant or benign character. Both malignant and benign tumors (BPH) can be treated using a highly specialized catheter system with built-in electrode and temperature control, and the treatment uses counter electrode(s) in the appropriate

EHY-2000plus

The EHY-2000 is the classical system for loco-regional deep oncothermia applications. This series has been used for treatment throughout the world for more than 20 years. Popular, versatile device, applicable for all kind of tumors.

EHY-3010 ML



The EHY-3010 ML is designed for the simultaneous multi-local treatment of advanced, metastatic disseminated, malignant and solid tumors. Within the range of Oncothermia systems, it is the pioneering breakthrough in the field of multi-local tumor therapy. Due to its highly flexible application electrodes (textile electrode), almost all tumor locations can be treated, even as large as the whole-body covering.

R&D:

Androtherm

This device is devoted for andrological treatment, mainly for the Peyronie's disease. Its special applicator and precise targeting uses the apoptotic effects combined with the plack-distortion with high efficacy. The penis curvature and the connected erectile disfunction treated with success by this device.

LabEHY

These kinds of devices are devoted for precise laboratory works in-vitro and in vivo research. The in vitro experiments can cover all the suspension and confluent layer systems, while the in vivo applicators are constructed for mice and rat experimental models. The device has revolutionary tuning system to follow even the extremely quick changes (like heart-rate of the animal), and extremely precise power adjustment. Temperature control and feedback measurements are also possible with the devices. All experiments can be completely documented electronically including the biological and electrical data.

VetEHY

These devices are developed for pet (cats dogs) treatment starting with a few dekagram to few tens of kilograms animals. Two devices are developed: one for the standard veterinary practice and pone for the veterinary research. Both have temperature measurements for precise documentation. Devices are equipped with data-handling and evaluation software.

ECT

This is the classical invasive device using pure electric-field invasively (needle application) or non-invasively (surface electrodes are applied). The precisely targeted tumor by the modulated electric field destroyed mixed way of necrotic and apoptotic processes. It is applicable for near-surface and easy-to-reach deeper tumors both in human and veterinary applications.

Accessories:

Temperature measurement unit

It measures the temperature intratumoral or extratumoral locations as well as on the surface of the skin. It is RF-independent even as high as 700W RF-power. Its sensitivity is 0.1 C, calibrated in the 36-55 C interval. The sensors are especially made for this purposes by Tateyama Kagaku, Japan.

Electromagnetic field sensor

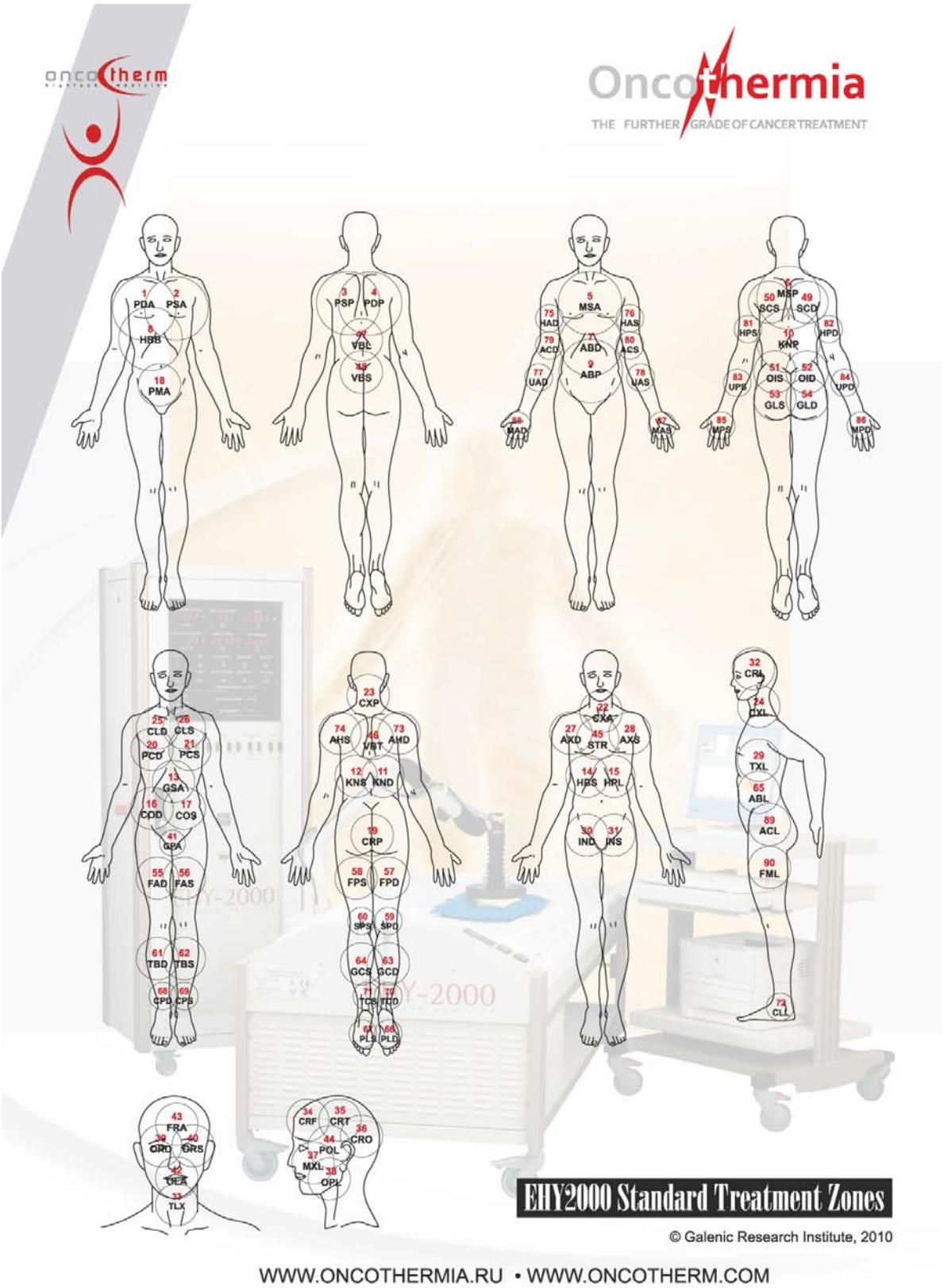
This devices is for the electromagnetic field detection. Useful accessory for all the oncothermia devices.

WEB-BOX

This device is a versatile adapter of the communication of any of Oncotherm devices to the web. It is data-safe and especially certified for medical data-security.

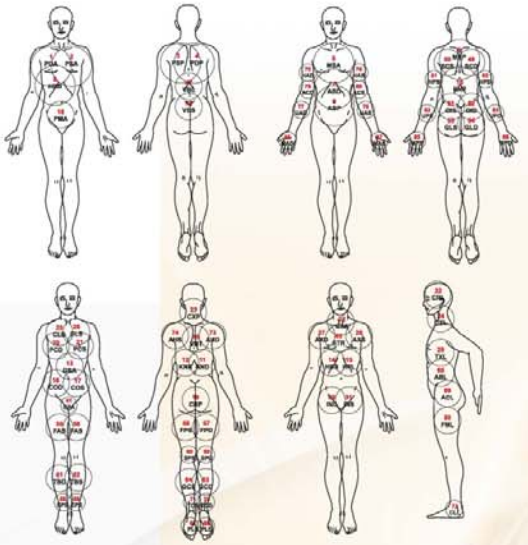
www.oncotherm.com

PI-03: Oncothermia.ru (2012) EHY-2000 standard treatment zones



Oncothermia
THE FURTHER GRADE OF CANCER TREATMENT

Summary Guidelines



EHY2000 Standard Treatment Zones

SUMMARY OF ONCOTHERMIA APPLICATION

Applicator

Applicator size should match the application zone and tumor size. Applicator is applied to the skin directly or through a thin fabric. In case of external fistulas, ulcers or weeping, applicator is applied through a thin moisture-absorbing paper. Applicator should be applied to that surface of the body which is closer to the tumor. Heating is the most effective at the 3-15 cm distance from the active (upper) applicator. Applicator should cover the entire projection of the tumor and adjacent lymph nodes, if possible. Applicator should be parallel to upper surface of the couch (neutral electrode), if possible. If it's impossible, the angle between the applicator and the couch should be as small as possible and open toward the nearest wall. The entire surface of water bolus should be in a tight contact with the skin without any air interlayer. Loose contact between applicator and skin leads to energy losses, reducing the heating efficiency and increasing the likelihood of burns. Applicator should be fixed firmly but without unpleasant pressure to the patient. Only water bolus should contact the patient. Applicator body (black) and RF cable shouldn't contact patient's body as it may cause burns.

Position of the Patient

Patient position should provide the shortest distance between the upper applicator and the tumor. In deep tumors, the preferable position is that one where there is a minimum layer (between upper electrode and the tumor) of the following structures (in descending order of importance) a) fat, b) bone and c) neural structures. The posture should be comfortable to allow the patient to sustain it during entire procedure. The basic patient position is lying on his back. If the tumor is located closer to the dorsal surface of the body, the patient is laid on his stomach. Some tumor localizations require lateral position (head, neck, etc.) During the procedure, the patient, if possible, should be immovable.

Treatment Zones

On the human body, there is a finite number of treatment zones. Each zone is designed to act on specific organs. For each treatment zone, there are certain recommendations on the size of the applicator, power and mode of exposure. The map of the treatment zones is shown on the left. The table of treatment zones and modes of exposure is shown below (top number is the treatment time, lower number is MRP). The complete list of the treatment zones and modes of exposure in accordance with ICD10 is contained in Annex B for the Technology."

Power

EHY2000 PLUS maximum power is 150 W. Applied power depends of applicator size.

Size	Ø, cm	MSP, W	MRP, W	MSP, W	MPP, W
Small	10	25	80	120	140
Standard	20	40	120	150	150
Big	30	60	150	150	150

- **MSP - Minimum Start Power:** the power which does not cause pain in 99% of patients. Pain at MSP is a contraindication for oncothermia treatment.
- **MRP - Maximum Recommended Power:** the power limit, above which the balance shifts towards classical hyperthermia, reducing the effectiveness of non-thermal mechanisms. Below MRP, the possibility of side effects and complications is minimal (less than 3%). MRP value may vary in different tissues and organs.
- **MSP - Maximum Safe Power:** the power, above which the likelihood of surface tissues burns increase provided incorrect use of applicators. It is allowed to exceed MSP level only in the presence of a trained doctor and under his/her responsibility.
- **MPP – Maximum Permitted Power:** the power which is safe subject to highly qualified application. MPP application is justified when tumor is resistant to lower powers.

In practice, the principle of oncothermia treatment is «maximum tolerable power».

Maximum Tolerable Power (MTP) is an individual patient parameter, the threshold power of pain. Exceeding of MTP is associated with a high probability of adverse effects, particularly superficial and subcutaneous burns. MTP is an individual and dynamic variable. Typically, MTP increases during the treatment course and a session in view of adoptation of tissues to oncothermia impact. Usually the adoptation is completed in 3-9 sessions, but sometimes (rarely) MRP can not be reached. In this case the power should continue at MTP, increasing the duration of the session according to the following calculation:

$$t' = tMTP + (t' - tMTPM) * MRP/MTP,$$

were *t' – scheduled duration of the session; t' – corrected duration; tMTP – time to reach MTP*

Increment and Interval of power Increase

Oncothermia is targeted for continuity of heat-up, not to reach of the maximum «plato» temperature. Therefore, the increase of power is carried out gradually and incrementally. The gradual increase of power also allows tissues to adapt to higher temperatures and reduces the toxicity of the method.

Recommended increment of power is 10 W, minimum 5 W, maximum 20 W. Recommended interval of power increase is 10-15 minutes, minimum 5 minutes, maximum 20 minutes.

Modulation

Modulation is applied by default. Poor tolerance of oncothermia treatment is the only reason to disable modulation. It could happen mainly at brain treatment. In this case, the course should be started without modulation. Modulation starts gradually during the course, and then becomes constant. Adaptation of the patient to modulation is the target because it is modulation which allows to realize the full effect of oncothermia.

Duration and termination of a session

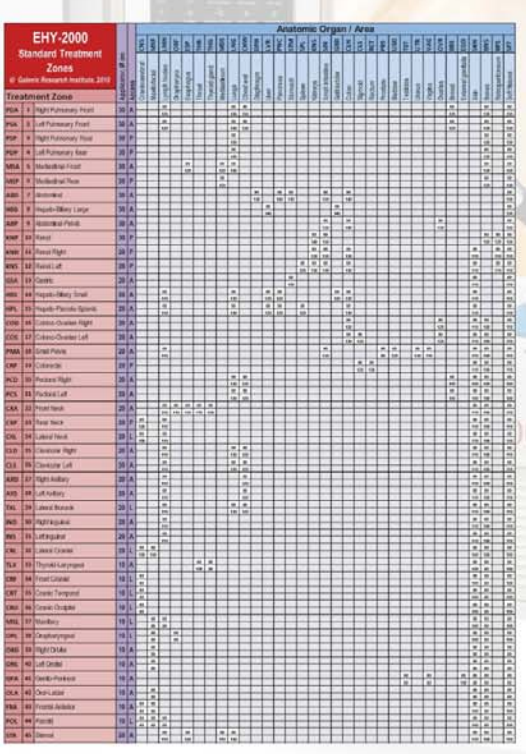
Standard duration of a session is 40-60 minutes for small applicator, 60 minutes for standard applicator and 90 minutes for big applicator. A session could be terminated after reach of scheduled time or dose. Maximum duration of a session with dose termination is 120 minutes.

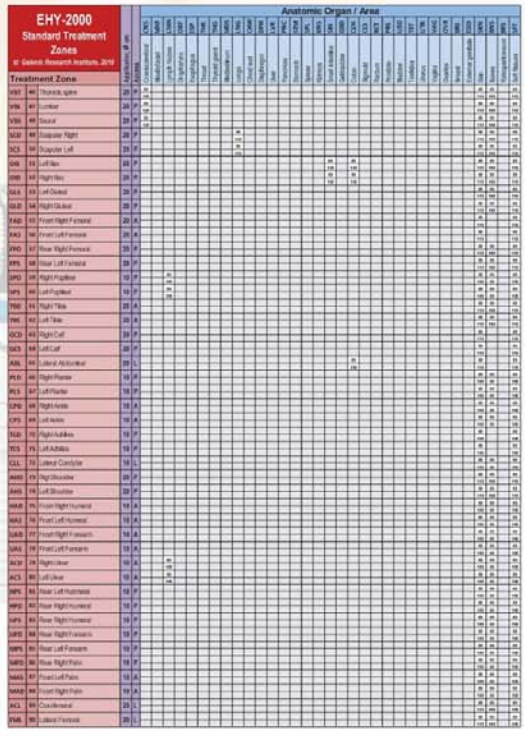
Interval between sessions

Recommended interval between sessions is 1-3 days (2-3 times a week). If necessary, the interval could be extended above 3 days. In combined treatment (chemo- and radiopotentiation), an interval between sessions is determined by the basic treatment. Daily use is possible.

Number of sessions and duration of the course

The average course consists of 6 treatments. The standard recommended course is 10 sessions, the minimum effective course is 5 sessions. The number of sessions for combined use (chemo- and radiopotentiation) is defined by a protocol of the basic treatment. Recommended course of oncothermia as a monotherapy is 15 sessions and more. The maximum number of sessions is unlimited. The longest described course for multiple liver metastases lasted for of 1030 days with more than 200 oncothermia sessions.





WWW.ONCOTHERMIA.RU • WWW.ONCOTHERM.COM

© Galenic Research Institute, 2010

Specialty Committee of Natural Therapy of World Federation of Chinese Medicine Societies (WFCMS)

World Federation of Chinese Medicine Societies (WFCMS) is an international academic organization voluntarily formed by group members in the world of Traditional Chinese Medicine and Natural Medicine. Currently, WFCMS has 220 society members in 58 countries and regions.

World Federation of Chinese Medicine Societies- Specialty Committee of Natural Therapy (WFCMS-SCNT) was established in May 2011. It aims to improve the world (regional) exchanges and cooperation between Natural Medicine groups, to raise the professional skill level of Natural Medicine practitioners, and to make positive contributions to human health. WFCMS-SCNT is based in Clifford Hospital of Guangdong Province which has the largest International Natural Medicine Center equipped with most comprehensive programs in the world.

Warmly welcome domestic and overseas personage experienced in Natural Medicine to join WFCMS-SCNT, and to visit International Natural Medicine Center .

Clifford Hospital International Natural Medicine Center

In May 2011, the First Meeting of The International Academic Conference on Natural Medicine was held in Guangzhou, China. Over 400 scholars from nearly 30 countries and regions attended the event.

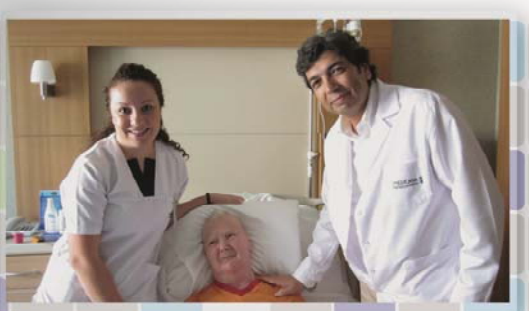
Professor Clifford L.K. Pang, Chairperson of World Federation of Chinese Medicine Societies – Specialty Committee of Natural Therapy (WFCMS-SCNT) together with Andras Elek Szasz, Vice Chairperson of WFCMS-SCNT, and Stefan Matthias Heckel-Reusser, Executive Director of WFCMS-SCNT.

Address: Clifford Hospital, 3 Hongfu Road, Panyu, Guangzhou, Guangdong, PRC.
Post code: 511495
Website: http://www.clifford-hospital.org/Hospital%5F09/cn/znwen/
E-mail: WFCMS-NaturalTherapy@clifford-hospitol.org zrlfwyh@126.com
Fax: 0086-020-84518400

PI-06: Oncotherm (2012) Welcome poster

PI-07: Osmanoglu Hospital (2012) Oncology Center Istanbul

ONCOLOGY CENTER ISTANBUL
Osmanoğlu Hospital



Şişli Osmanoğlu Hospital is located in the heart of İstanbul, Sisli -İstanbul – Turkey. Şişli Osmanoğlu Hospital has 21 medical services. Oncology Service has 2 medical oncology physicians, 3 oncology nurses, 1 laboratory assistant , 1 coordinator and 1 secretary. The clinic works as a day clinic. Medical oncology physicians are Prof. Dr. Bülent Berkarda and Dr. Salih İyikesici.
Şişli Osmanoğlu Hospital Oncology Service has started doing hyperthermia treatment on July 2011 with Oncotherm EHY - 3010. They installed second Oncotherm EHY – 3010 device in the beginning of February 2012.

Prof. Dr. B. Berkarda
Onc. Dr. M.S. İyikesici

- Cancer Coaching
- Cancer Prevention
- Conventional Chemotherapy
- Metronomic Therapy
- Insulin Potentiation Therapy
- Hyperthermia

They usually apply hyperthermia with chemotherapy or hyperthermia alone. Only few of their patients had hyperthermia with radiotherapy. Also, some of them have insülin potentiation therapy (IPT).
They focus almost all of solid cancer types.
The physicians usually use the protocol of ten times one hour each.

onco therm
high tech medicine

TEK GRUP
SAĞLIK HİZMETLERİ A.Ş.

PI-08: Seong Gi Min (2012) A case of clinically complete remission of lung with hyperthermia and concurrent 5th-line chemotherapy in a disseminated NSCLC patient

Zenith 제니스병원 HOSPITAL

A case of clinically complete remission of lung with hyperthermia and concurrent 5th-line chemotherapy in a disseminated NSCLC patient

Seong Gi Min, MD, Zenith Hospital, Seoul, Republic of Korea

Backgrounds

Lung cancer is the leading cause of cancer death worldwide. With combination chemotherapy, the median survival is 8~10 months. Besides chemotherapy, various modalities have been evaluated to get better survival. Hyperthermia is a new therapeutic approach and has synergistic effect with chemotherapy to control the disease and to improve the survival. Some clinical characteristics , i.e., female, adenocarcinoma, and never-smoker, show good prognosis. However, the efficacy of 5th-line chemotherapy for disseminated NSCLC is doubtful. Recently, we experienced the excellent response of one case of lung-to-lung metastatic NSCLC being clinically nearly complete remission of lung with hyperthermia (EHY-2000) and concurrent 5th-line chemotherapy.

Case presentation

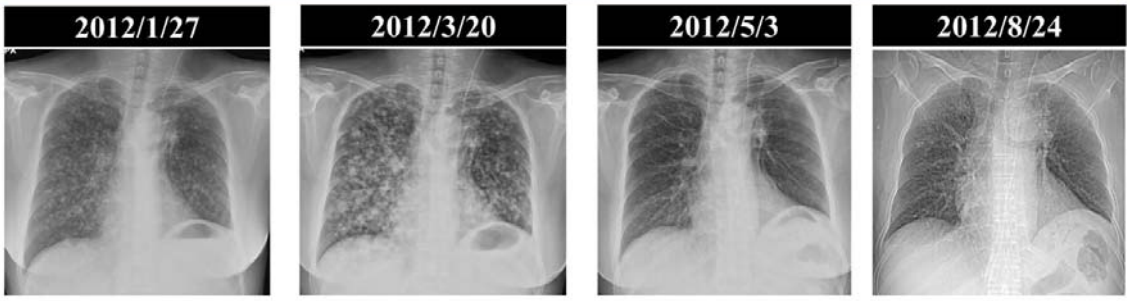
Patient : Female/53, never-smoker

Pathology, lung: adenocarcinoma, EGFR mutation (-) *The date of diagnosis:* May, 2007

Current status: metastases to lung-to-lung, brain, bone, pleura

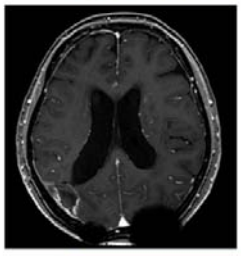
Past medical history & present illness: She had received LUL lobectomy on May/17/2007 followed by adjuvant CCRT. In May, 2009, the recurrence, brain, lung and bone metastasis was developed. After GKS on May/27/2009, palliative chemotherapy was administered. Those chemotherapeutic regimens were gemcitabine/cisplatin, gefitinib, and pemetrexed from August/3/2009 to November/3/2011. In June, 2011, she also had received craniotomy & tumor removal of right parietal lobe followed by whole brain radiotherapy (November/22-25/2011). Since January 2012, an agent in clinical trial had been administered. With progressive disease, the agent was switched to 5th-line palliative chemotherapy, docetaxel on March/21/2012. Hyperthermia, EHY-2000 system (Oncotherm GmbH, Troisdorf, Germany) had been applied on her chest since February/7/2012. *After 3rd cycle of hyperthermia, clinically nearly complete response was observed on chest X-ray and chest CT.*

Conclusion: The concurrent therapy of hyperthermia and chemotherapy would be promising in disseminated NSCLC.



Agent in clinical trial (2012/1/27-3/20) Docetaxel (2012/3/21-2012/8/24)

Hyperthermia (2012/2/7-2012/7/9)

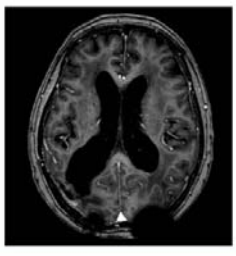


Metastatic Brain Tumor

June/ 2011
Controlled
Hydrocephalus with
Ommaya reservoir

Metastatic Brain Tumor

August/2012
Aggaravated
Hydrocephalus &
Leptomeningeal seeding



Non Hyperthermia