Oncothermia is a kind of oncological hyperthermia – a review

Szigeti GYP, Szasz AM, Szasz O

Innovation Center, Semmelweis University, Hungary (szigeti.gyula@med.semmelweis-univ.hu)
Cancer Centre, Semmelweis University, Budapest, Hungary
(szasz.attila_marcell@med.semmelweis-univ.hu)
Department of Biotechnics, St. Istvan University, Godollo, Hungary
(biotech@gek.szie.hu)

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Abstract

Oncothermia is a personalized type of hyperthermia, which selectively heats malignant cells, thermally targeting the nano-sized parts of their membranes (rafts). It raises the temperature of these clusters of transmembrane proteins by more than 3 ºC relative to their environment. The heated cells mostly die by apoptosis. The thermal damage starts to produce damage-associated molecular patterns (DAMPs), including the expression of HSP70 and HSP90 on the cellular membrane, the expression of the TRAIL DR5 death receptor and the release of HMGB1 and massive amounts of HSP70 into the extracellular matrix, producing vast numbers of apoptotic bodies. Together with this thermally induced complex process, the overall temperature rises due to heating of the selected parts. This temperature increase under in vitro conditions could be as high as to denature the proteins in a meat phantom, but under physiological conditions, it is at least 3–4 ºC, as indicated by invasive measures, both in animal and human studies. Our objective is to concentrate on the definite thermal behaviour of the oncothermia method, reviewing the resulting thermal effects, which ignite all the biomolecular changes mentioned above.

Keywords

Oncothermia, modulated electro-hyperthermia, temperature, in silico, in vitro, in vivo, preclinical, human

Introduction

The definition of hyperthermia varies by source. Commonly, "hyperthermia is the use of therapeutic heat to treat various cancers on and inside the body" [1]. Medicine.net defines the process of hyperthermia as overheating of the body [2], which is the method of whole-body hyperthermia. The various definitions differ by the target in the case of local hyperthermia. The National Cancer Institute (USA) defines the target as the cancer tissue:

"Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F)" [3]. This definition (with a tissue target but defining the cellular aim) is used by Wikipedia as well: **"**Hyperthermia therapy is a type of medical treatment in which body tissue is exposed to slightly higher temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anti-cancer drugs" [4].

The American Cancer Society (USA) defines the target as cells: "When cells in the body are exposed to higher than normal temperatures, changes take place inside the cells. These changes can make the cells more likely to be affected by other treatments such as radiation therapy or chemotherapy" [5]. The Medical Dictionary defines no target; only the temperature rise: "a much higher than normal body temperature induced therapeutically or iatrogenically" [6].

Despite the evidence of nano-range heating at the membrane [20], [31], [35] and the large-scale successes [29], [30], as well as publications [66], [65], practitioners of hyperthermia demand to see thermal effects and temperature developments. OncoTherm has taken a great interest in this project and has shown the requested temperature elevations under physiological conditions in animals and human studies, which will be published soon. Due to the frequent demands for data, we are presently showing some model experiments, as well as animal and human measurements of temperature rise in oncothermia.

Oncothermia defines hyperthermia more provisionally, emphasizing targeting of malignant cells: Oncothermia is a kind of hyperthermia, which selectively heats malignant cells to a higher temperature than that of their environment [7]. The discussion is not centered on the higher

temperature, (which is always the basic condition), but the definitions differ only in the target of heating.

The main difference is, of course, in the homogeneity of heating (temperature). The most homogeneous heating occurs in whole-body hyperthermia. It has extreme (over 40 °C) and mild (under 40 °C) versions. The local heating is, of course, non-homogenous, because only a part of the body is heated, while the blood (which also circulates over the tumour) remains at body temperature. Hyperthermia attempts to mimic the whole-body version, requiring homogeneous heating in the target as much as possible (this is the CEM [cumulative equivalent minutes] concept). Of course, by the time local (regional) treatment approaches whole-body heating, because local heating also heats up the environment. The source of the heat is the heated tumour.

Targeted therapies are a new trend in oncology. Many conventional oncologic therapies have been combined with targeted liposomal [8] or nano-particle [9] supportive therapies or radiotherapeutic interventional nano-radiation [10]. Personalization has also become a new target [11], considering the biocomplexity [12] and considering the new goals of pharmaceutical products [13]. Immune stimulation and modulation have become one of the hottest research fields [14]. These trends are focused on safe and effective treatment using the latest biomedical and biotechnical knowledge.

The original idea for local hyperthermic cancer treatment was based on real thermal targeting, focusing on the local tumour. So, targeting is not a new concept in hyperthermia. Considering precise targeting, there are many hyperthermia methods not using homogenic heating. The best example of inhomogeneity is thermal ablation. Targeting with thermal-sensitive liposomes [15] and nano-particles is a long-term goal [16]. Finally, nanoparticles are the heat absorbers: these are heating targets, and the complete tumour is heated non-homogeneously. The sources of heat to raise the temperature of the complete tumour is a dispersed set of nano-particles placed in the tumorous lesion. Hot nanoparticles heat up their environment – the tumour itself.

Change of paradigm: oncothermia

Oncothermia follows the trend of selectively targeting heterogeneous malignant tissue, heating existing natural nanoparticles (as in the case of dispersed nano-suspensions). However, the nanoparticles targeted by oncothermia are naturally presented, clusters of transmembrane proteins (membrane rafts). This explains the "nanothermia" name, which started to be used for this inhomogeneous heating.

Oncothermia uses various biophysical effects to select and heat up tumours, the malignant cells inside them and their membrane rafts. Macro-selection to find the tumour (self-focusing) is based on the Warburg effect. The high glucose metabolism of the tumour (which is also the basis of positron emission tomography (PET) diagnosis) provides a high ionic concentration in the tumour. Consequently, the tumour has high electric conduction, so the applied radiofrequency (RF) current flows automatically through the tumour. This emphasizes that macro-selection efficacy is highly correlated with diagnostic PET signals.

Selection is performed inside the tumour on a micro-scale to find the malignant cells. The dominant biophysical character of the malignant cells is that these cells are mostly autonomic. These have no connection with their neighbours (broken adherent bonds and broken junctions), whereas their healthy counterparts are part of a network. This means that the extracellular electrolytes around

the malignant cells differ greatly from the matrix around their healthy counterparts. This could also be recognized by a well-chosen electric field.

The third selection factor is nanoscopic and represents the energy-absorption itself. Clusters of transmembrane proteins (membrane rafts) have entirely different radiofrequency absorption than the surrounding membrane. This makes it possible to distinguish them and forces them to absorb most of the energy in the rafts (nanothermia) [17].

Together with the above topological selection, oncothermia applies dynamic selection. This refers to modulation, which selects by the modified dynamic properties of malignant cells compared with their healthy counterparts. The action of modulation is a definitive part of the subject of fractal physiology and mainly based on stochastic resonance.

The points of action of modulation, in short, are as follows:

- The topology of the biological tissues shows characters of the tissue and its possible diseases (topic of pathology). The tissue patterns that the pathologist evaluates by her/his expertise can be itemized and evaluated mathematically by fractals. This topologically characterized method is the part of the fractal physiology.
- The geometry of the pattern definitively determines the interactions (dynamics) of the cells involved in the structure, described by spatio-temporal dependence of the fractals. This is, of course, opposite in nature: the dynamics determines the pattern. Due to the diagnostic reality, which starts with pattern evaluation, we face the inverse problem: start with the structural results.
- The spectral density (dynamics) of homeostatic (healthy) patterns always shows exponential dependence of the f frequency, with exponent (-1), so the dependence is reciprocal, 1/f. Consequently, the dependence of the logarithm of spectral density on the logarithm of f shows a straight line with a slope of (-1). This is the fingerprint of the complexity (self-organizing behaviour). When complexity is "normal", the dynamics are healthy. When complexity is broken (deviation from 1/f dynamics), the interactions of the cells are out of homeostatic control.
- The pattern differences between healthy and malignant tissues make it possible to distinguish them. The forced healthy dynamics (1/f modulation) are an easy fit to healthy tissues, but are in disharmony with malignant ones. The effect could be pressing the precancerous (not malignant yet, but going to be malignant) cells to find their correct dynamic connections (social signals in the tissue through the re-established cadherins and junctions), or the disharmony could be so huge that it cannot be done.
- When the malignant cells are not able to find their way back to homeostasis, they absorb a finite amount of energy from the external constrains of the 1/f modulated field, which is concentrated on the clusters of transmembrane proteins (rafts), which initialize signal pathways for DAMPs, ICD and consequently, APC and T-cells (CD4+ and CD8+), (abscopal effects). These are strongly connected to immune effects, which are also intensively investigated worldwide [18].

The main point of targeting is to select where the energy must be absorbed. This is by far not a simple task in the technical reality, due to the inhomogeneity of the target. A large target is very non-homogenous in its composition and mainly in its thermal properties. Heat conduction and heat convection depend on blood perfusion and the development stage of the tumour, so equal energy absorption does not produce equal temperature. Furthermore, the inhomogeneity changes over time: homeostatic control starts to cool down the overheated volume, causing an even greater

thermal discrepancy in the tumour. This selective specific absorption rate (SAR) is the basis of the focus and the long-term challenge facing technical realization. Unfortunately, any very accurate energy deposition in the target does not mean that the temperature is also accurately fixed in that point. Despite the focused energy, the temperature varies over time in a natural way, heating up the non-targeted tissues by thermal conduction and thermal convection. The main heat-delivering process is governed by blood flow, which is anyway "responsible" for equalization of the temperature in a homeostatic manner.

Oncothermia is a kind of hyperthermia. Following the modern trend of oncology, it is personalized [19]. Oncothermia is devoted to targeting the nano-parts of the malignant lesion and selecting the malignant cells [20], targeting them by thermal energy in the nanoscale region [21], inducing natural apoptosis [22] in cancer cells and boosting immune protection mechanisms [23] accompanied by an abscopal effect [24].

Oncothermia follows a special hyperthermia concept, trying to avoid the problems of conventional hyperthermia. The conventional methods induce physiological feedback (increased blood flow), which is a technically intensive heat exchanger and could cause huge biological challenges. The two main problems are connected to the definite delivery by intensified blood perfusion, which supports tumour growth, and the intensive blood flow could increase the risk of malignant invasion and dissemination starting a competition between the lethal thermal effect and the supporting blood supply [25]. This is the main disadvantage of conventional hyperthermia. This disadvantage, of course, does not exist in vitro. The results of massive research activity conducted in vitro are misleading due to the missing physiological feedback.

To avoid these problems, hyperthermia should be applied only as a complementary therapy: its application as a monotherapy (diathermia) is contraindicated. The conventional treatment is combined with drastic radio- or chemotherapies, causing numerous side effects as we well know. With oncothermia therapy, Natural approaches are very effective in oncothermia therapy. Due to the minimized negative feedback from blood flow makes monotherapy applications of oncothermia possible [26].

This suppressed negative feedback from blood flow does not mean that oncothermia is non-thermal. Oncothermia is a kind of hyperthermia when we concentrate our heating on the cellular membrane. This heating is very intensive but very local [27], and so the physiological feedback caused by the intensification of blood flow is less effective. The oncothermia solution concentrates on the selection of malignant cells and heating up their cell membranes instead of the complete tumour mass [21]. The main problems of the complementary applications of hyperthermia in oncology is solved in this way [31]. This heating method has numerous advantages: the overall temperature could be low (while the nano-range heating is high), and the thermal cytotoxity is effective [28].

Thermal damage starts to produce damage-associated molecular patterns (DAMPs), including the expression of HSP70 and HSP90 on the cellular membrane, the expression of the TRAIL DR5 death receptor and the release of HMGB1 and a massive amount of HSP70 into the extracellular matrix, producing a vast number of apoptotic bodies. Together with this thermally induced complex process, the overall temperature rises from the heated sources of the selected parts.

These effects were followed from the basic laboratory to clinical applications [29], [30], [31]; they fit completely with the modern trends of oncotherapies. The theoretical background of oncothermia uses the complexity of homeostatic equilibrium [32] (fractal physiology [33]), but its technical solution is not simple [34], [35].

Despite its differences with hyperthermia [36], oncothermia is based on thermal effects, but the temperature distribution is far from equilibrium [37], [38]. The temperature effects of oncothermia

were reviewed previously [39], [40], but our current objective is to show a summary adding new results and reviewing the real-time temperature growth in actual studies of various conditions.

The membrane-associated nano-temperature on membrane rafts was calculated in silico [44] and was measured and will be shown by direct indication [77] and by conventional flow cytometry methods [78]. Extended preclinical temperature measurement was shown on a living pig when its liver is targeted by oncothermia [92]. The fact that oncothermia is a kind of hyperthermia is proven.

Oncothermia creates nano-heating so that the complete effect is centred on the electromagnetic selection of the membrane rafts of malignant cells. This special targeting causes the average temperature to increase over time. Fig. 1.

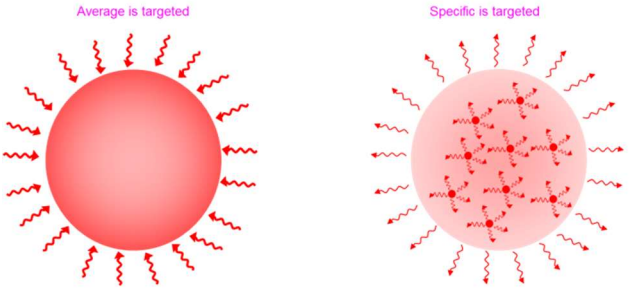


Fig. 1. The nano-scaled targets are heated, and those will heat up the complete volume

The precise focused energy does not mean the focus of the temperature, because it is naturally spread out. After a defined period, the temperature is almost equalized, and the special selection is lost.

Fig. 2.

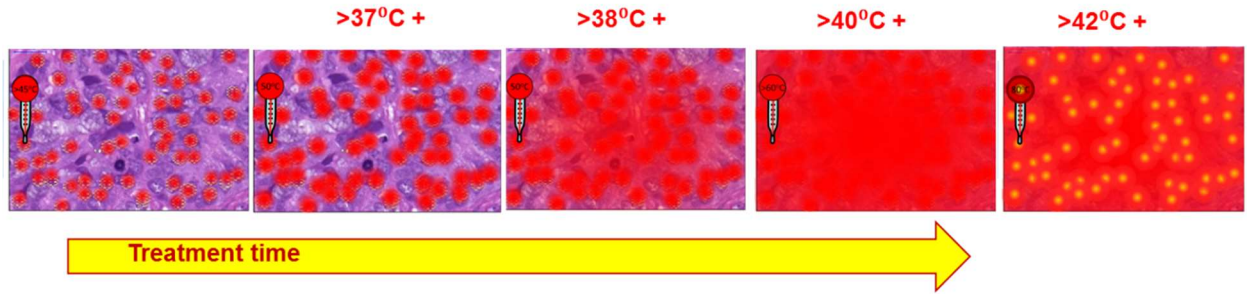


Fig. 2. The selected nano-parts heat up their complete volume, and the selection weakens over time.

The model system of heating is the extreme heat on rafts, which heats up the cell and the tumour at the end. The tumour heating is usually in the range of mild hyperthermia. Fig. 3.

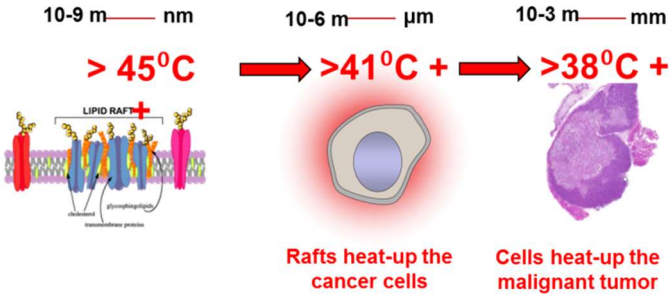


Fig. 3. Sequential heating makes the temperature on rafts extra high and that on the complete tumour mild.

The critical membrane state could cause special signals of instability. Indeed, the transition temperatures and critical fluctuations in giant plasma membrane vesicles (GPMVs) were well measured in vitro [41].

Oncothermia research is a complex process, which begins with ideas and follows with theoretical elaboration, in silico research, in vitro experiments, in vivo model-research, preclinical studies and finally, clinical applications. However, this line is multi-directional, having various feedback mechanisms modifying all steps of the processes, Fig. 4.

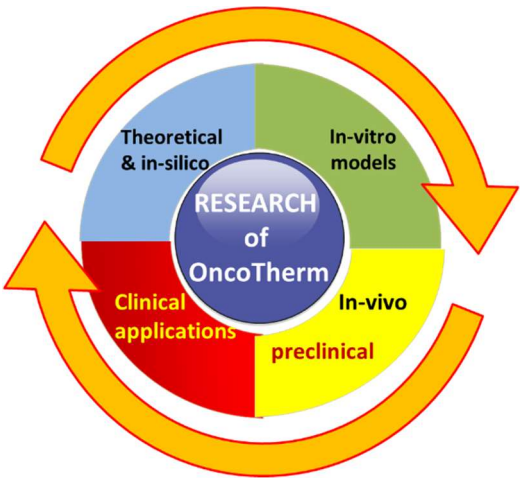


Fig. 4. The complexity and interdependence of various levels of the research

We concentrate on the heating effect of oncothermia determining the appropriate dose for the process. The goal is to show the special thermal effects of oncothermia method, showing its connection with the conventional hyperthermia therapies.

Methods

The general demand for experimental proof of the thermal effects and the temperature developments of oncothermia remain high among professionals. Oncotherm has taken a keen interest in this project and has shown the requested temperature increases in silico, in vitro, in vivo and under physiological conditions, providing preclinical (animal) and human studies.

The early in silico models were generated by MathCad programs and were later performed by computer simulation technology (CST) software, [42], developed for such hyperthermia treatments [43]. The finite integration technique (FIT) was used to solve the appropriate Maxwell equations with a low-frequency domain solver (EQS) module. Open boundary conditions were fixed at 13.56 MHz. Tetrahedral mesh (adaptive division) was for numerical calculation with an accuracy of 10^{-6} [44], [45]. The cell model used a 10–15-μm cell diameter, a 0.2-μm raft diameter, a 20-nm raft thickness and a 5-nm membrane thickness.

The phantom models were made with realistic materials: high-protein-content eggs and mixed meats, as well as liver, which showed the higher temperature clearly by changing its colour. Temperature measurements were also made by fluoro-optical sensors (Luxtron), and the application of mixed, chopped meat/fat phantom mimicking the thickness of the fatty human body (for measuring energy penetration) made possible the most realistic target in the topic.

In vitro and in vivo systems are used for measurement by various laboratories, and sample temperature is well controllable everywhere with a few Watts of power and using fluoro-optical temperature measurement (Luxtron). We show here only the results of our own measurements.

Animal measurements were made on the tumours of dogs, and experimental temperature measurements were also made on pig livers, making sure that the physiologic feedback compensation effect did not wash out the temperature elevation.

Human temperature measurements were made on sarcomas, ovary, breast and abdominal cavity. The highly specialized sterile temperature sensors were based on thermocouple platinum-iridium-rhodium materials.

Results

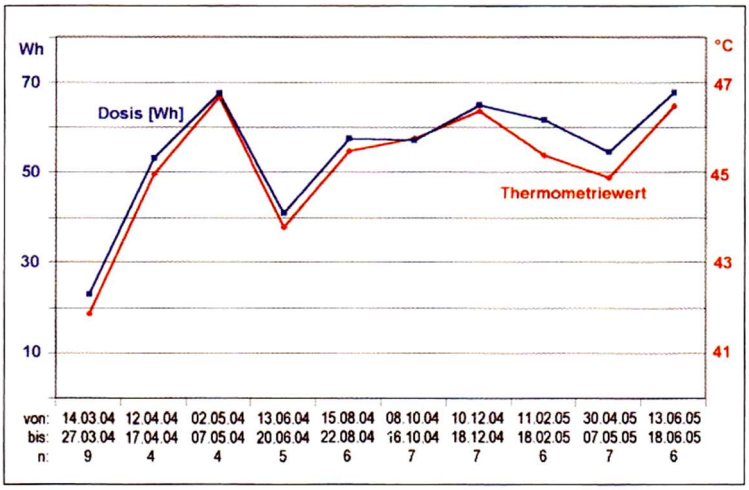
Studying the thermal actions of oncothermia, we published a couple of papers on the dosing of oncothermia [46], [47], and a generalized theory has been formulated [48]. We have shown the importance of the Arrhenius law in oncothermia as the definite fingerprint of thermal effects.

In silico we have made a model to show how the electrical field from the electrode is transferred to the target area. The main results are:

- Automatic focusing of the electrical field on tumorous areas [49], [50],
- Concentration of the electrical field in the lipid rafts on a nanoscopic scale [51],
- Calculation of temperature increase due to RF field used by OncoTherm [52], [53], [54], [55], [56],
- Deep heating with small power is possible [57], [58],
- Auto focusing of electrical field to components with higher conductivity [59], egg + liver [60].

Phantom models

The first method of approval was the conduction of measurements on various phantom models made in the beginning era of device checking. Temperature development was, on average, in the centre of the measurement, as seen in the figure below. The correlation is strong and so the calibration of the equivalent temperature is controlled and proven [61]. Fig. 5.



Mittelwerte von eingebrachter Energiedosis und Thermometriewerten

Fig. 5. The correlation of the calculated equivalent temperature in tumour-phantom and the applied dose

Numerous thermo-camera pictures were made of specialized impedance phantoms as shown below. Fig. 6.

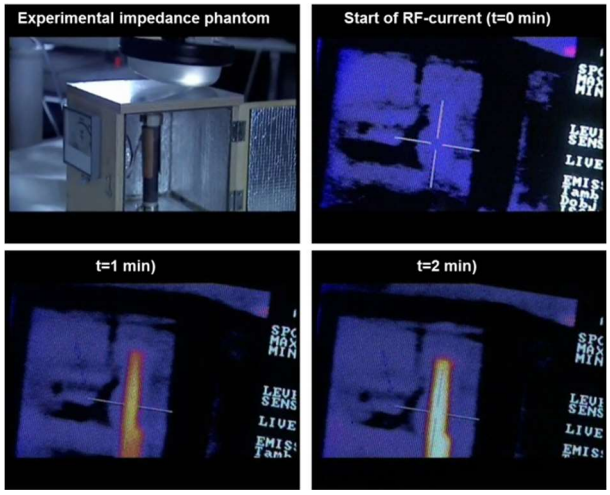


Fig. 6.

Carbon impedance in a thermally isolated box, measuring the calibration of the power of the device. The intensive temperature increase is due to the isolation, concentration of heat on the target, lack of heat conduction and convection of radiation loss to the environment.

The fruit treatment shows the temperature increase as well, Fig. 7.

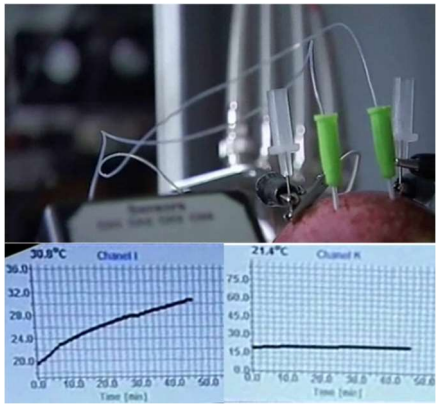


Fig. 7. A simple apple experiment showing well the heating of the apple measured inside of the fruit.

More realistic phantoms could be "constructed" out of protein structures such as eggs.

It was demonstrated in real time experiments at conferences how we can easily reach 60 ºC in the middle of the tumour model (egg white) without heating up the surrounding materials [62]. We have shown the selective and very intensive heat effect at the ICHS conference in real life: we heated up the egg white until it coagulated in water. Our colleagues were participating and could see with their eyes that the water was not heated up, but the egg-white became "hard", which meant that its temperature was over 60 °C. This is a selection on its own, because the overall temperature (water + egg) was not too high: it increased by only a few degrees. Therefore intensive mass cooling cannot stop the nano-heating on the membrane, and we have higher cytotoxicity at a lower average temperature compared with conventional hyperthermia at a higher average temperature. Fig. 8.

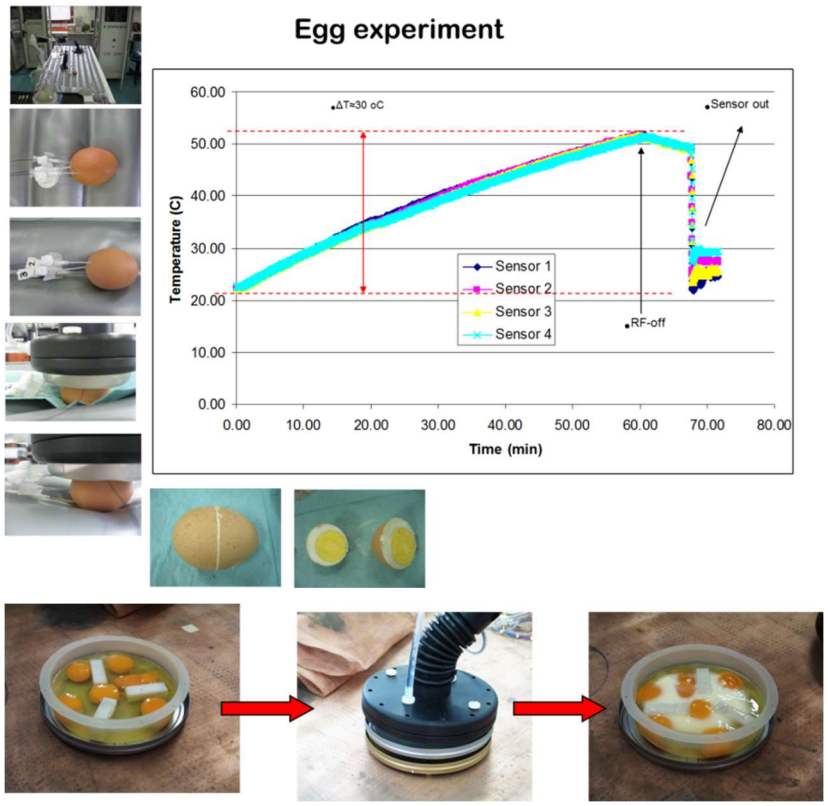


Fig. 8.

Extreme high temperature is trivially demonstrated by "cooking" or "frying" the egg with simple RF current at 150 W. The temperature increase is so great that it causes coagulation of the protein (>50 ºC).

It is more peculiar when the egg white is in a water tank. The water is not heated, but the egg white coagulates (starting from inside!), clearly showing the selection mechanism. Fig. 9.

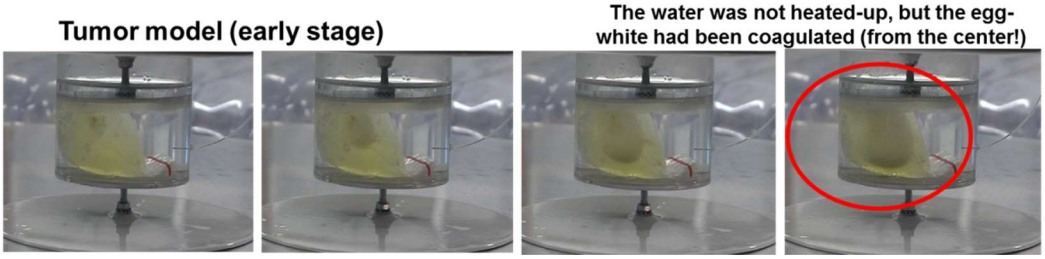


Fig. 9. The water temperature only increased slightly, but the egg white temperature inside was greater than 50 ºC, starting protein coagulation in the middle of the specimen. Thus, targeting is proven.

The same was also shown clearly when the liver was "cooked" inside, while outside, it did not show any changes. Fig. 10.

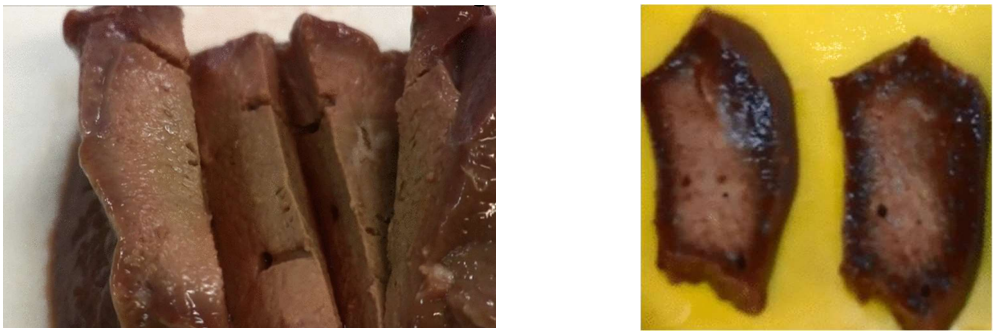


Fig. 10. The liver is "cooked" inside, while the outside is "fresh". This again shows the selection capability of the RF-current induced by EHY2000 device.

Models (mimicking the cancer region) showed the validity of this focusing [63]. Fig. 11.

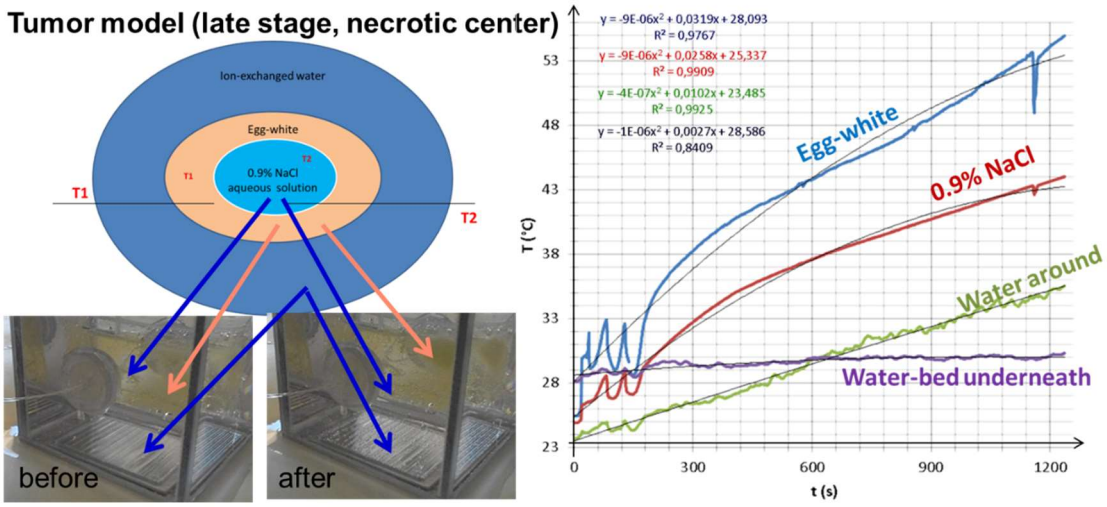


Fig. 11. Experimental results on a model of heterogenic heating

The simple meat (pork) treatment, mimicking the skin by polyethylene packing, was employed earlier on when the first TÜV approval was granted. The increase in temperature reached 5 °C in the bottom of the model (7 cm depth). It was important that we could focus the heat in the lower middle region where the gain was more than 6–9 °C [64]. In multiple replicate experiments, the results were convincing. Fig. 12.

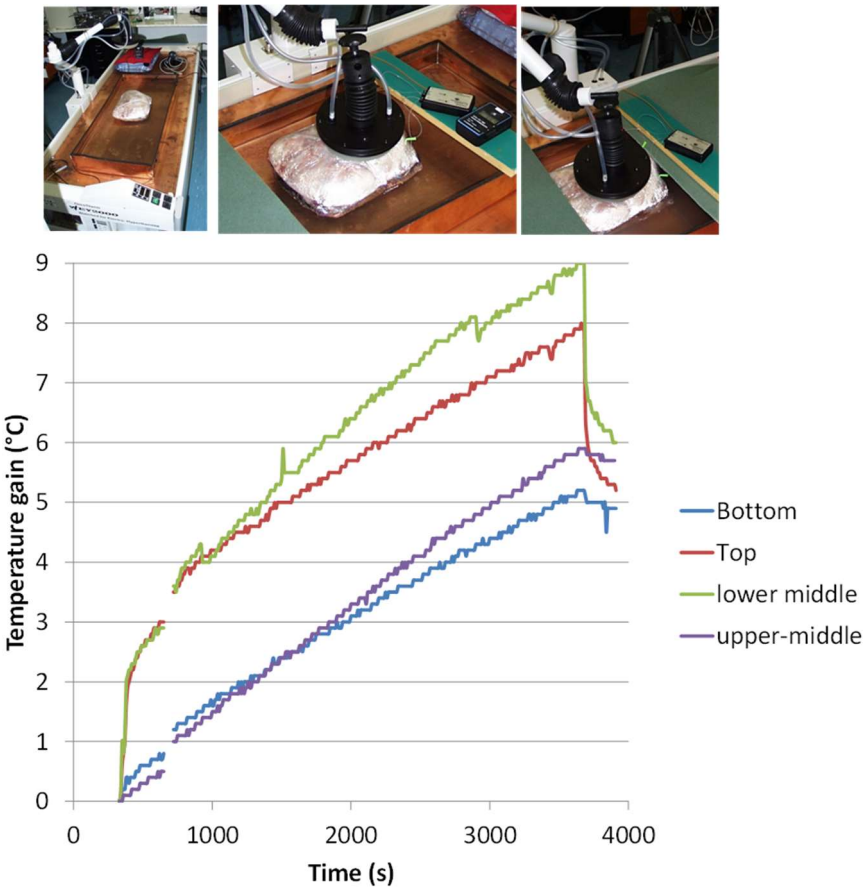


Fig. 12. A large piece (5.1 kg) pork meat phantom, wrapped in foil.

In multiple replicate experiments, similar results were obtained. Fig. 13.

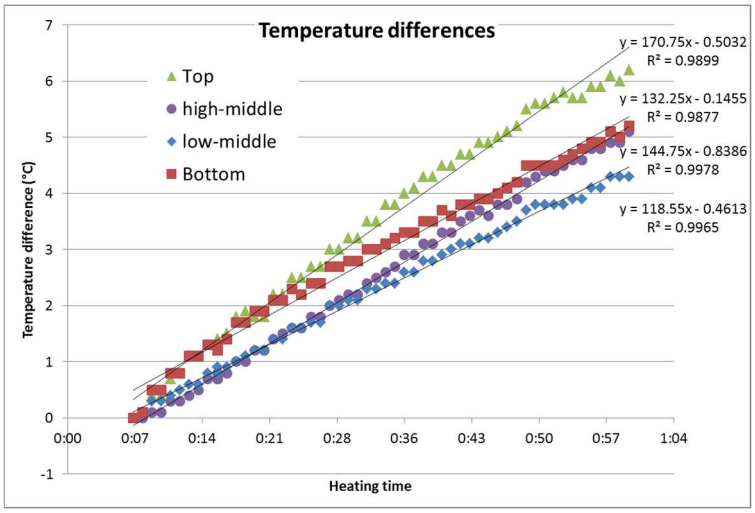


Fig. 13. Repetition of the previous (Fig. 12.) measurement.

A special meat phantom model was constructed to study the energy absorption in depth [65]. This deep temperature measurement of a meat phantom modeled the complete cross-section of a human body. The measurement shows well that, at a depth of 24 cm, the temperature increases by 19 ºC during 35 min by 100 W RF energy flow. Fig. 14.

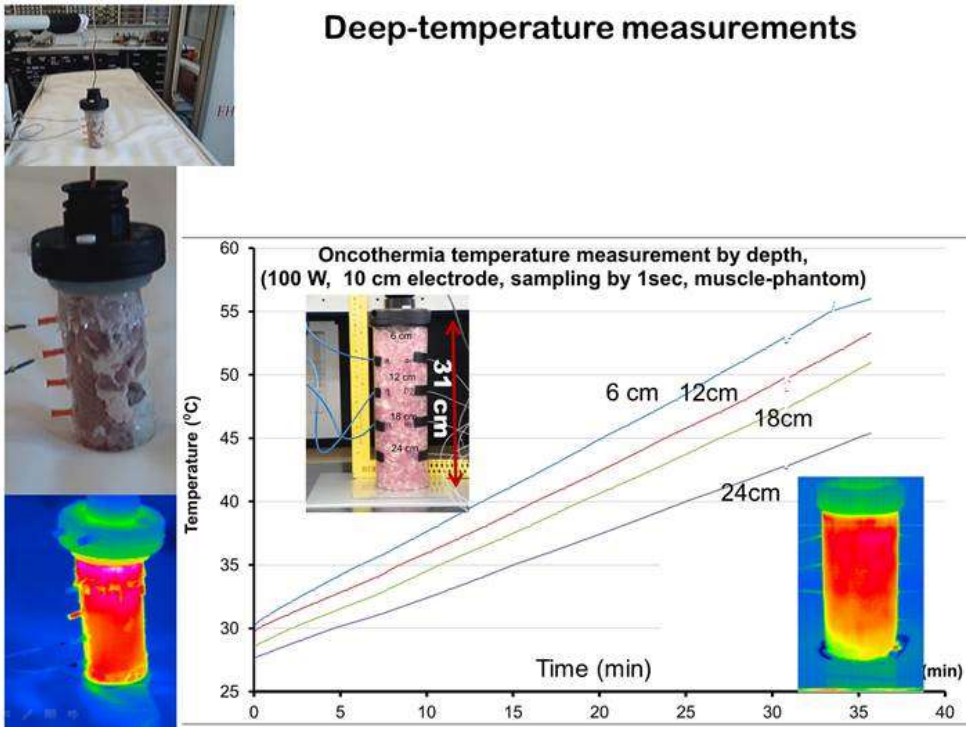


Fig. 14.

Meat phantom experiment for penetration measurement [65]

Layered meat phantom approaches the reality of the liver treatment measured by Prof. Herzog [66]. It is all well shown in the phantom: Fig. 15.

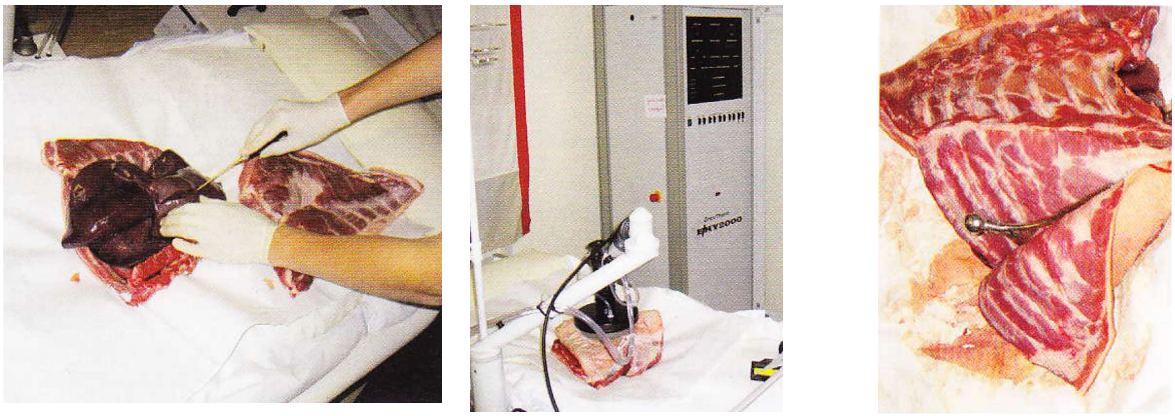


Fig. 15. Layered meat-phantom model: liver in piglet ribs and a limb prothesis

Modelling primary and metastatic tumours with a heterogeneous meat phantom [66]

The applied model shows well the temperature increase in the liver through the skin and ribs, even with a large metallic implant. Fig. 16. and Fig. 17.

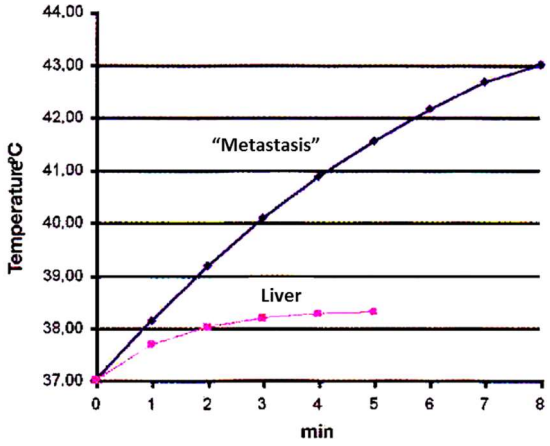


Fig. 16. Model of metastasis (◆) and liver heating when the arteria-hepatica delivers 0.32 l/min/kg blood through the liver (■). The applied power is 100 W.

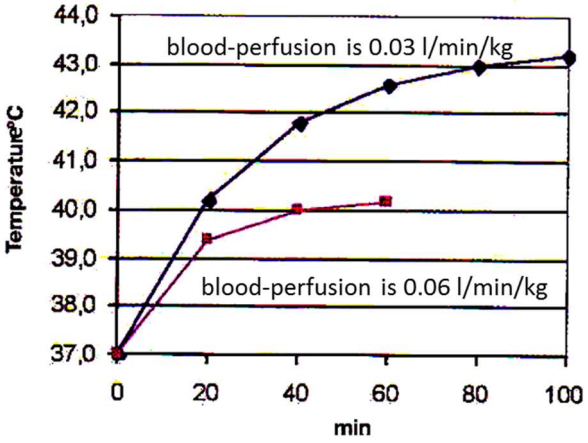


Fig. 17. Hypoxic model (◆, blood-perfusion is 0.03 l/min/kg) and normal perfusion (■, blood-perfusion is 0.06 l/min/kg)

The temperature increase is shown in the tables.

Measurement results after 15 minutes			
Measurement point		Temperature rise °C	
			(from - to)
△T	Skin	5.4	2.6 - 7.1
△T	Liver surface	4.1	2.6 - 5
△T	Liver inside	2.4	2.4 - 3.9

Hyperthermia measurement value on 100W after 26 minutes, and the temperature of a metal hip replacement which is between the skin and the ribs			
Measurement point		Temperature rise °C (from - to)	
△T	Skin	16.6	17.3
△T	Ribs	9.5	14.3
△T	Liver surface	7.9	8.5
△T	Liver inside	6.2	6.6
△T	Hip replacement	9.5*	
*Temperature is the same as the neighbouring rib tissue's temperature			

Graphical illustration is shown below in 3D. Fig. 18. and Fig. 19.

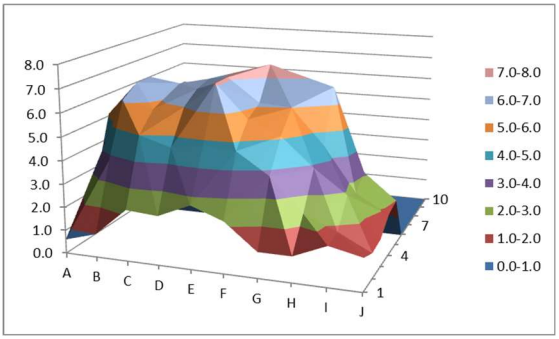


Fig. 18. The skin tissue by 20 cm electrode, 100 W; 15 min

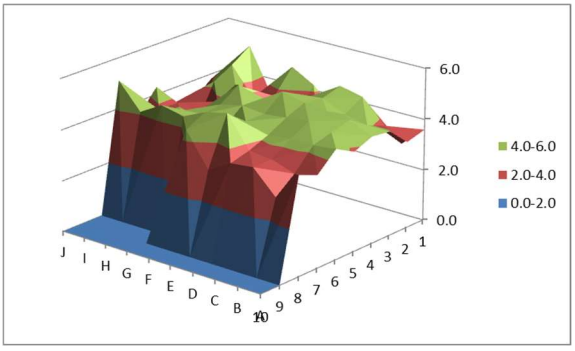


Fig. 19. Deep-seated liver, electrode 20 cm diameter, 100 W; 15 min

Piglet (without its harslet) is measured reaching a 12 ºC temperature increase with 100 W for 18 min. The piglet was packed in kitchen polyethylene foil to avoid further bleeding and to mimic more isolation of "fat skin" on its body surface. Fig. 20.

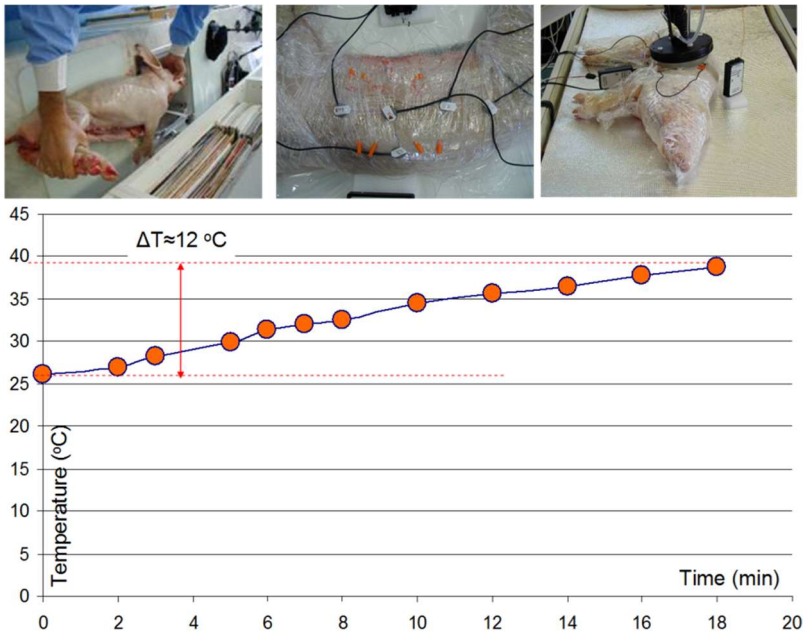


Fig. 20. Piglet measurement ex-vivo. (Wrapped in foil.)

In silico models

The early in silico models showed clear selection by the inhomogeneity of the tissue materials. Tumour tissue has higher conductivity [67] and a higher dielectric constant [68], which we used for electromagnetic selection. The in-silico calculation was made with MathCad. The strong selection (energy targeting) is theoretically proven by this calculation. Fig. 21.

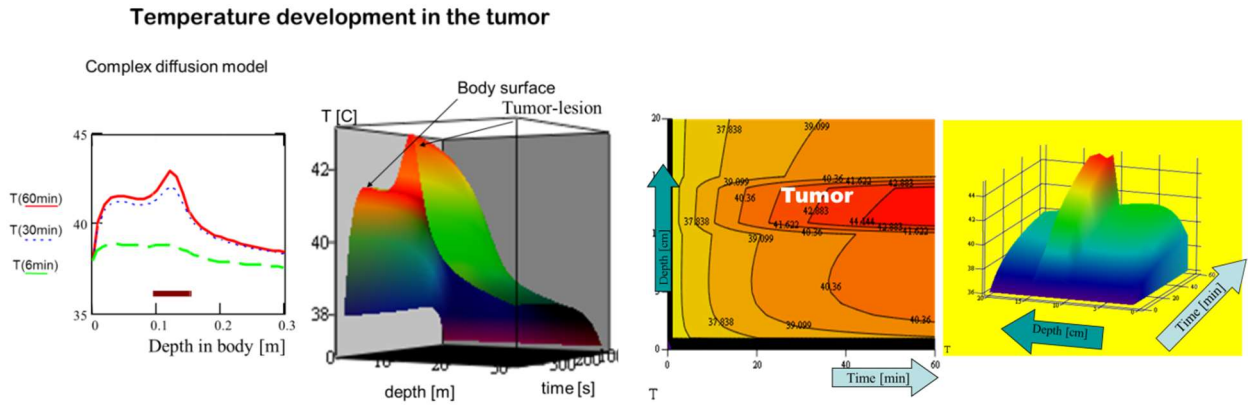


Fig. 21. The temperature increase is calculated by the impedance specialties of tumour tissue

Other in silico models were developed for micro-range differences in the tumour. The cell membrane contains clusters of transmembrane proteins (rafts), and those are targeted by oncothermia. The in-silico model calculated a layer of the rafts fitting its thickness into the membrane phospholipid bilayer (single-layer model) and more realistically, when it is thicker, making complex interactions with the electrolytes in their vicinity look like a layered system in the membrane (sandwich model). Fig. 22.. Fig. 23.

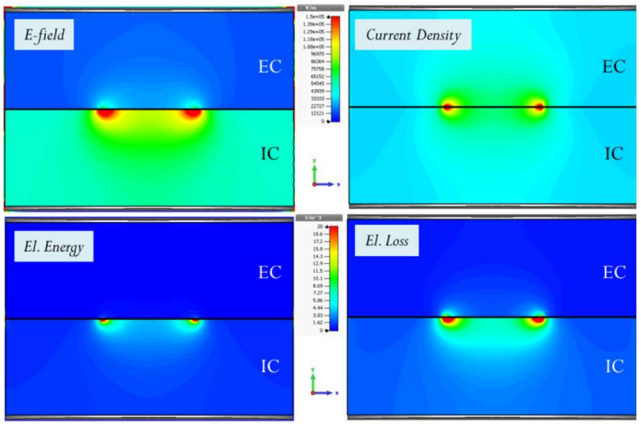


Fig. 22. Simple (single-layer) model

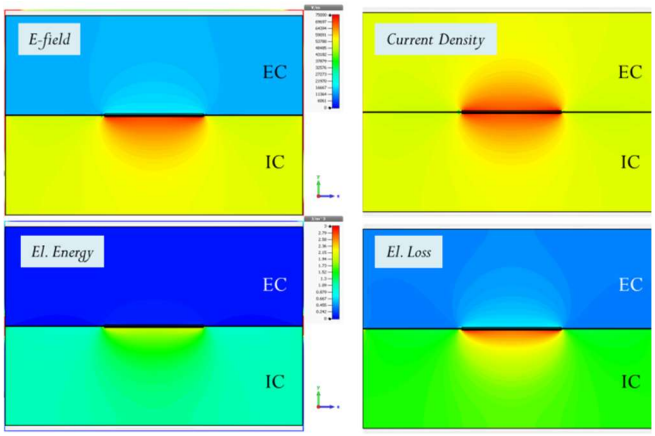


Fig. 23. Complex (sandwich) model

The calculation shows how targeting is effective at high temperatures in the nanoscopic range. The energy loss on the raft is significant. Fig. 24.

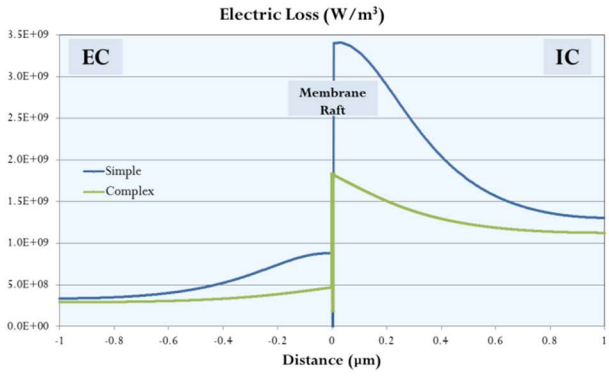


Fig. 24. Energy loss on the membrane rafts in the two models

The micro-domains have an even higher temperature gain when the contact between the cells amplifies the current density, causing energy absorption at these points. Fig. 25.

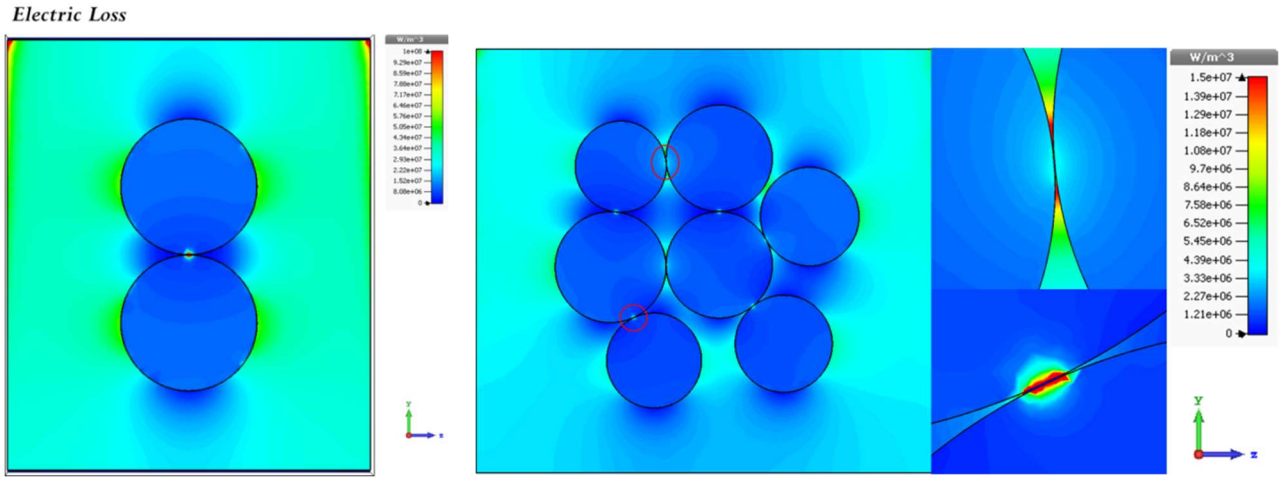


Fig. 25. Electric loss at the micro-domain connections

When the phantom and in silico models were summarized, two main parameters were shown. The first was the focusing of energy on the targeted area, which could also be proven in vitro by the co-culture experiments, showing that the in-silico model represents the in vitro model correctly.

Secondly, the energy placed in lipid rafts was shown in the in-silico model [69] , which correlated with the increased temperature in the cell membrane. In vivo models show that the cell membrane temperature in lipid rafts is about 3–6 °C higher [7], which means that more heat reaches those nanoparts.

In vitro models

We can show hyperthermia and the additional effects of the OncoTherm treatments on in vitro models. The following main issues are considered:

- Heating up cell lines to 42 °C is possible [70], [71],
- Positive effects of conventional hyperthermia and additional effects of the OncoTherm type of hyperthermia [72],
- Selective focusing on tumour cells without harming healthy cells [73],
- Calibration curve for the temperature vs killing rate of conventional hyperthermia and OncoTherm type of hyperthermia shows a 4-5-fold increase in effectiveness at the same temperature or the same effectiveness at a 3-centigrade lower temperature [74],
- Cell membrane temperature is on average 3-6 °C higher than average temperature [74], [75].

Many laboratories are working in vitro with oncothermia, conducting specialized research on the mechanism of cytotoxicity and probing the limits of its application [76], [77]. Typical temperature curves are linear applying a few watts of power in average. Fig. 26.

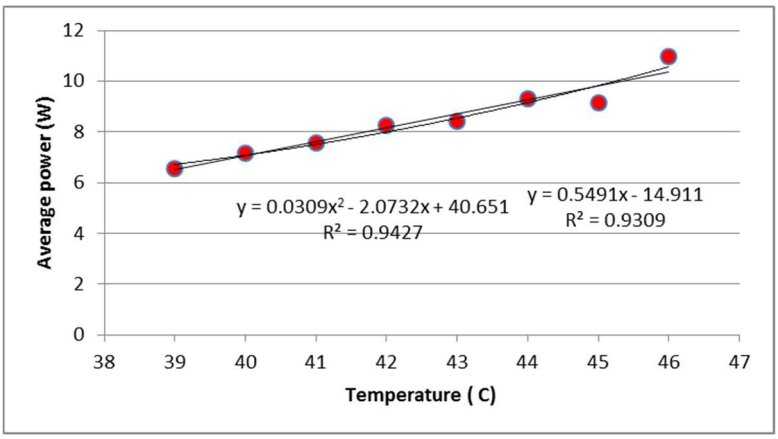


Fig. 26. Typical temperature curves shown for in vitro systems

In the early studies of molecular biology of oncothermia, the in vitro systems showed interesting results for E-cadherin, beta-catenin and other protein changes [29]. The newer results show the targeting specialty of oncothermia in vitro [78], [79]. Fig. 27.

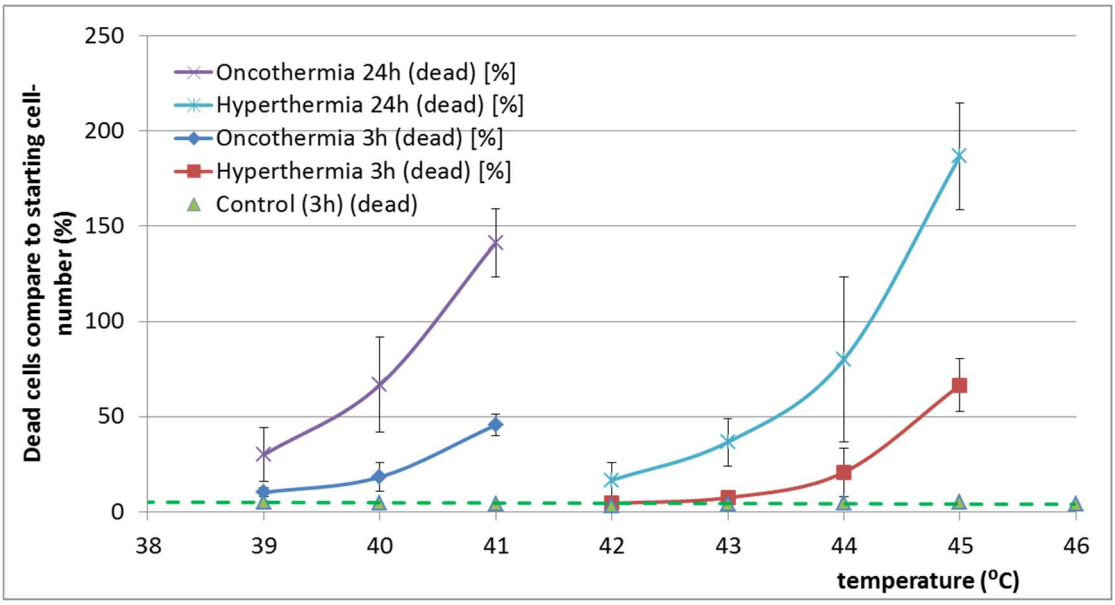


Fig. 27. The thermal effect of oncothermia acts much earlier than that of conventional hyperthermia [78], [79]. The error bars represent standard deviations.

The temperature dependence of cell death (U937, human histiocytic lymphoma cell line) is shown clearly. Conventional hyperthermia can be used to calibrate the temperature. According to this calibration, oncothermia produces a temperature at least 3 ºC higher in nano-targets than in the average electrolyte. This in vitro result corresponds well with the earlier measured in vivo results. Fig. 28.

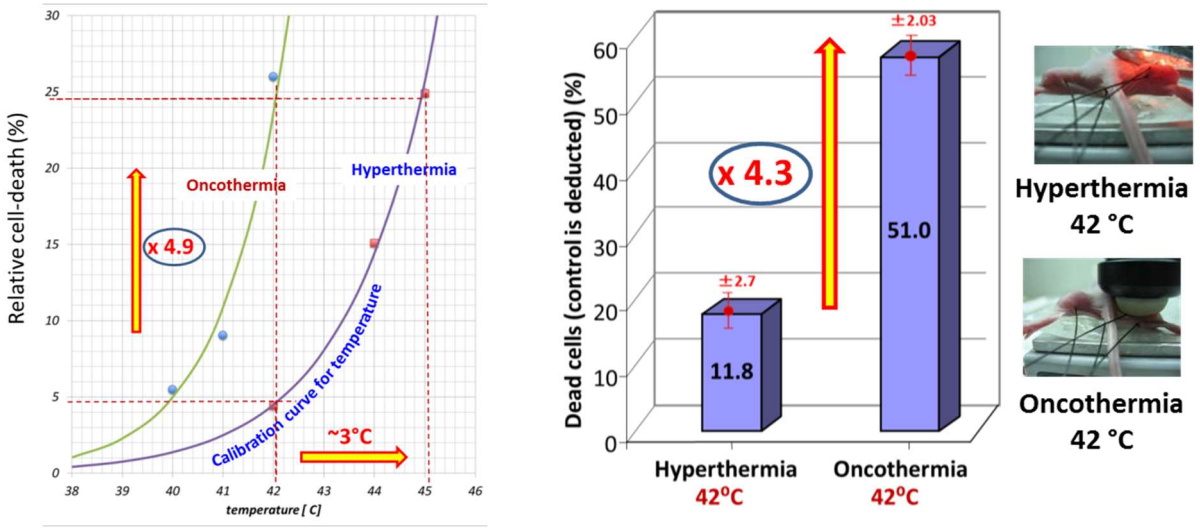


Fig. 28. Experiments show 4.9 and 4.3 times larger cell-distortion at 42°C than its conventional hyperthermia counterpart in vitro and in vivo, respectively

The in vitro and in vivo temperature results show about the same 3 ºC overheating of the nano-range targets compared with the average

This nano-targeting could be measured by the calcium influx by oncothermia. Fig. 29.

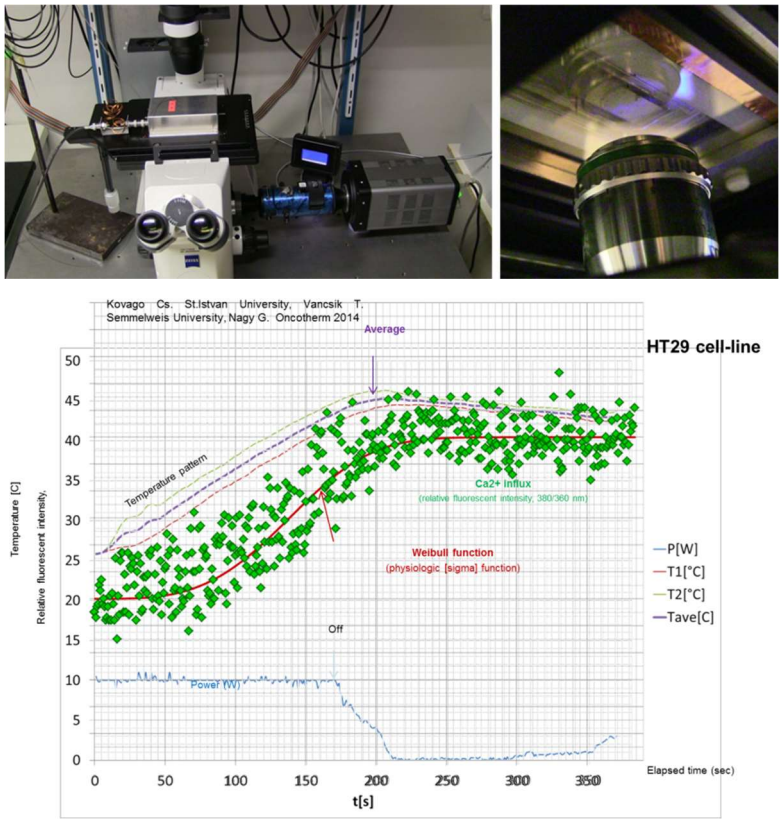


Fig. 29. The calcium influx follows the temperature well and is a good fit to the physiological Weibull curve in vitro in the HT29 cell-line

The change in calcium influx shows well the same shift that was measured in other experiments. Nano-heating is in action. Fig. 30.

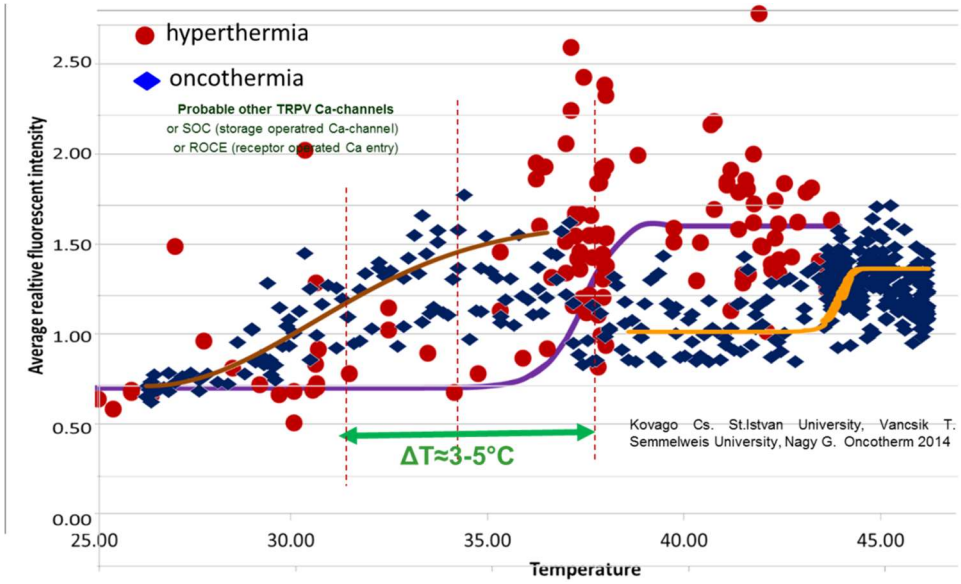


Fig. 30. The calcium influx in the case of the A431 cell line in conventional hyperthermia (♦) and in oncothermia (●) cases

Summarizing the in vitro measurements, the calibration of the cancer killing rate between conventional hyperthermia and the OncoTherm type of hyperthermia gives about the same percentage increase. This correlates with the theory that the temperature in the cell membrane is higher than the average cell temperature. Furthermore, the in vitro measurements provide a fairer assessment, showing biomolecular and immunohistochemical results, which lead us to the immune and abscopal effects in vivo.

In vivo models

- Heating up the target area to 42+ °C [80],
- Heating up the tumour in vivo to 42 °C is possible [81],
- Positive effects of conventional hyperthermia and additional effects of the OncoTherm type of hyperthermia [72],
- Selective focusing on tumour cells without harming healthy cells [82],
- Calibration curve of the temperature-killing rate of conventional hyperthermia and OncoTherm type of hyperthermia shows a 4–5-fold increase in effectiveness at the same temperature or the same effectiveness at a 3 °C lower temperature [71]

Numerous in vivo models were made and published during the era of research on oncothermia from the beginning of its applications [23], [22], [24], [38], [83], [84], [85], [86]. Some typical ones are shown below for nude and SCID mice. Fig. 31.

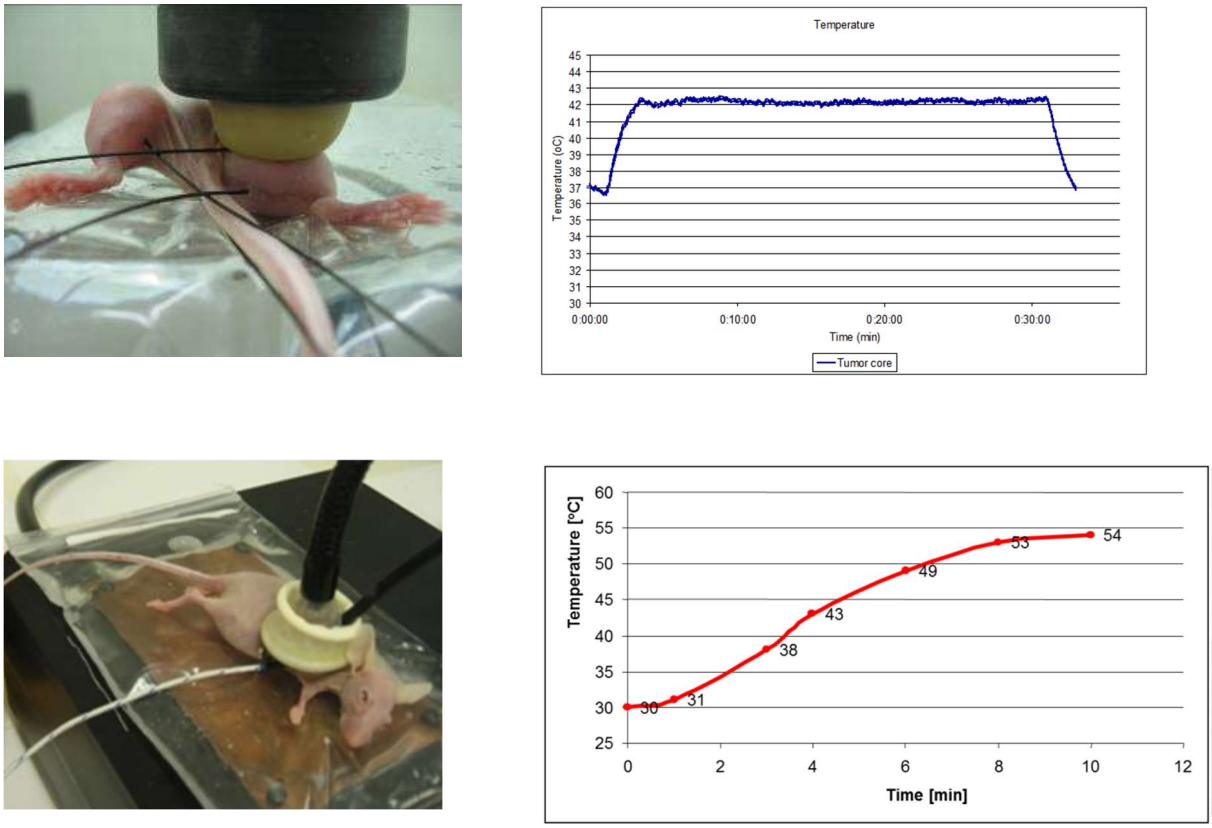


Fig. 31. Typical in vitro heating curve for nude mice allowing the temperature to be kept stable at 42 ºC. Test animal: HT-29 (human colon adenocarcinoma) cell line tumour bearing nude mice (Balb/C Nu/Nu); power: 8 W/6.4 W (SWR:1.5); Energy: 4.8 kJ/3.8 kJ

Experimental study with human medulloblastoma shows also definite temperature increase in the tumour Fig. 32.

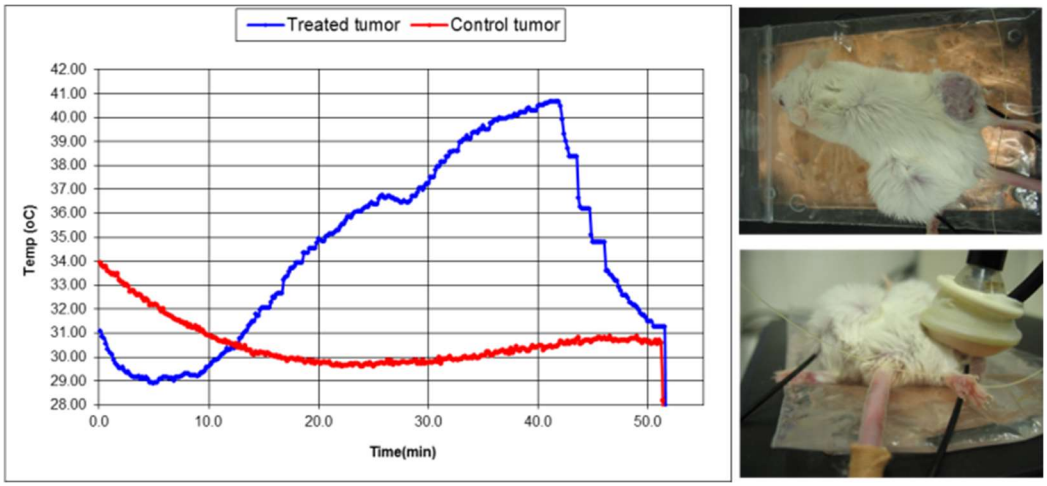


Fig. 32. Experimental animal: SCID mouse with human medulloblastoma tumour; Location of the tumour: femoral region, both sides; Radiopharmaceutical: 99 mTc labelled liposome (experimental product of the OSSKI); Injected dose: 35 MBq/0.1 mL 13 W/5 W (SWR = 2.1); 5 min (3.9 kJ)

The experimental animal model show temperature increase in the liver, Fig. 33.

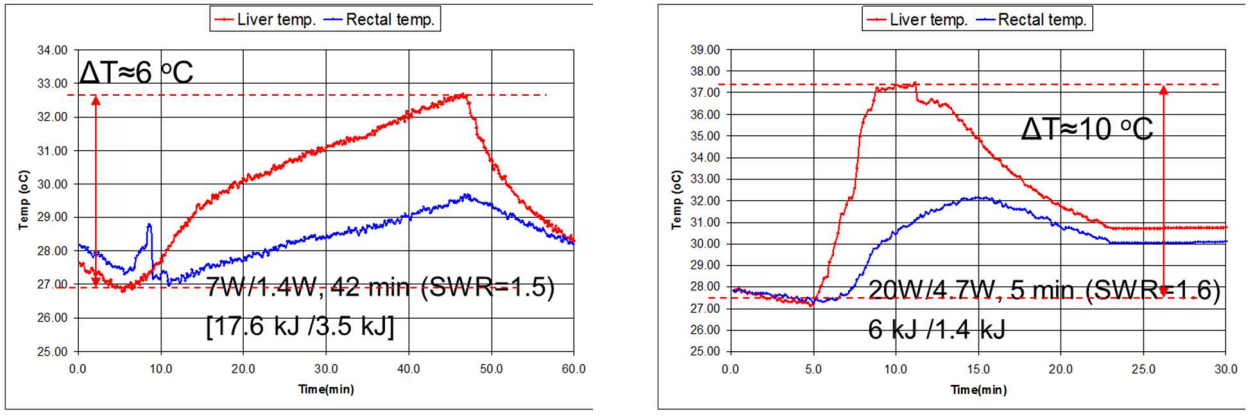


Fig. 33. Liver temperature of the mice. The gain in temperature is obvious.

Different electrodes were also tried for the best treatment performance. The bolus electrode and the flexible one are shown below. Fig. 34.

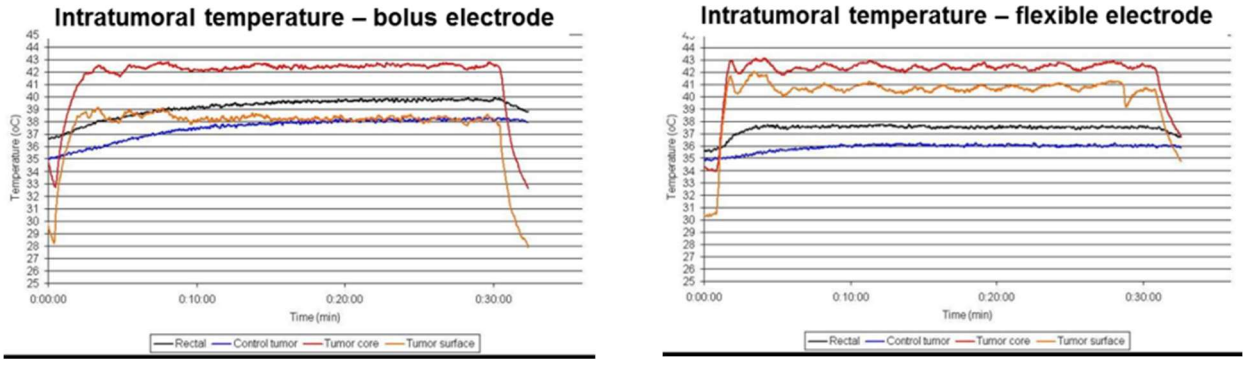


Fig. 34. Electrode comparison. The temperature is well controllable in both cases.

An important study was published [28], in which the macro-temperature was cooled down while the micro-heating (selective targeting) was active. In this way, oncothermia showed its superior efficacy under low macro-temperature conditions. Fig. 35.

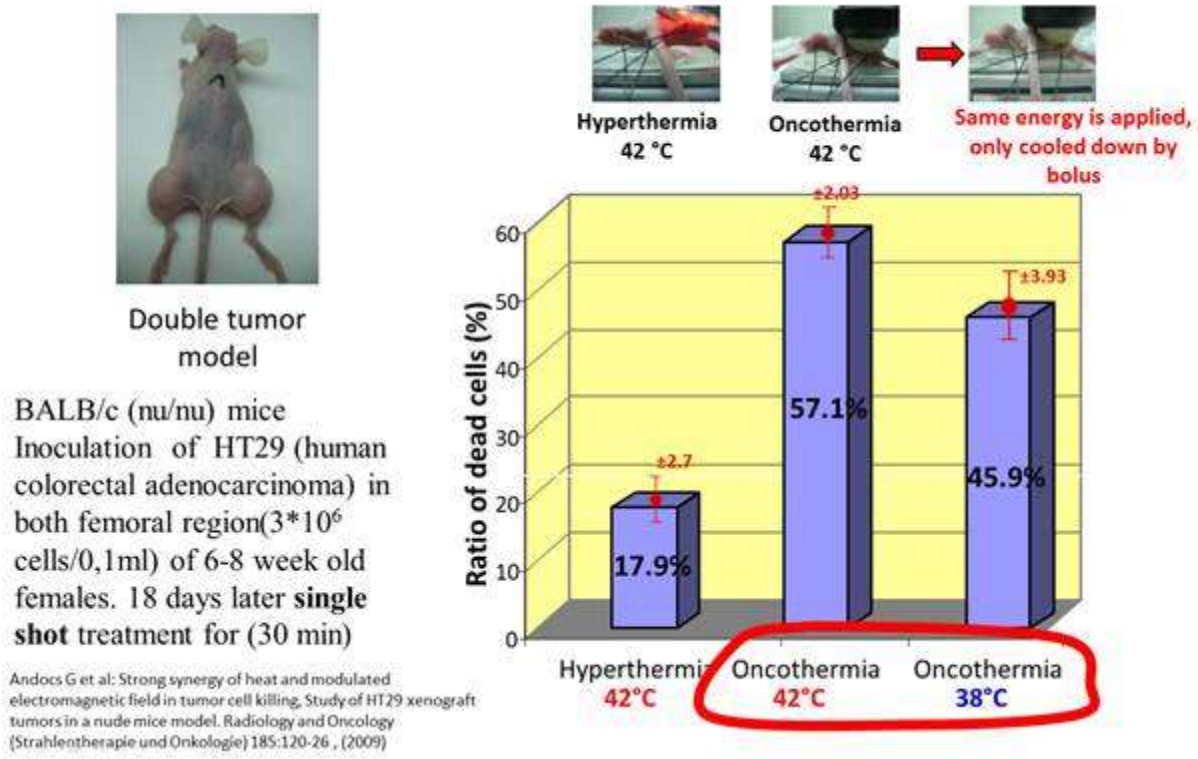


Fig. 35. Macro cooling only slightly affects cytotoxicity when micro-targeting is held constant.

This nano-technology uses natural (instead of artificial) nanoparticles on the membrane. The membrane effects have been shown in numerous molecular biology investigations over time [22], [23], [36], [38], [83], [84]. The effects on the membrane were measured with ultramodern immunohistochemistry and widely published: Fig. 36.

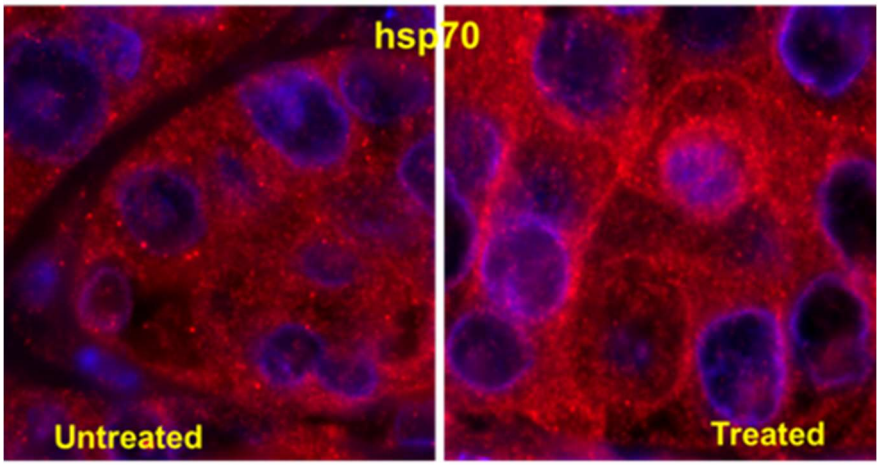


Fig. 36. HSP70 membrane expression [83]

An intensive membrane excitation special apoptotic process is induced, causing a massive "natural" programmed cell death. Fig. 37.

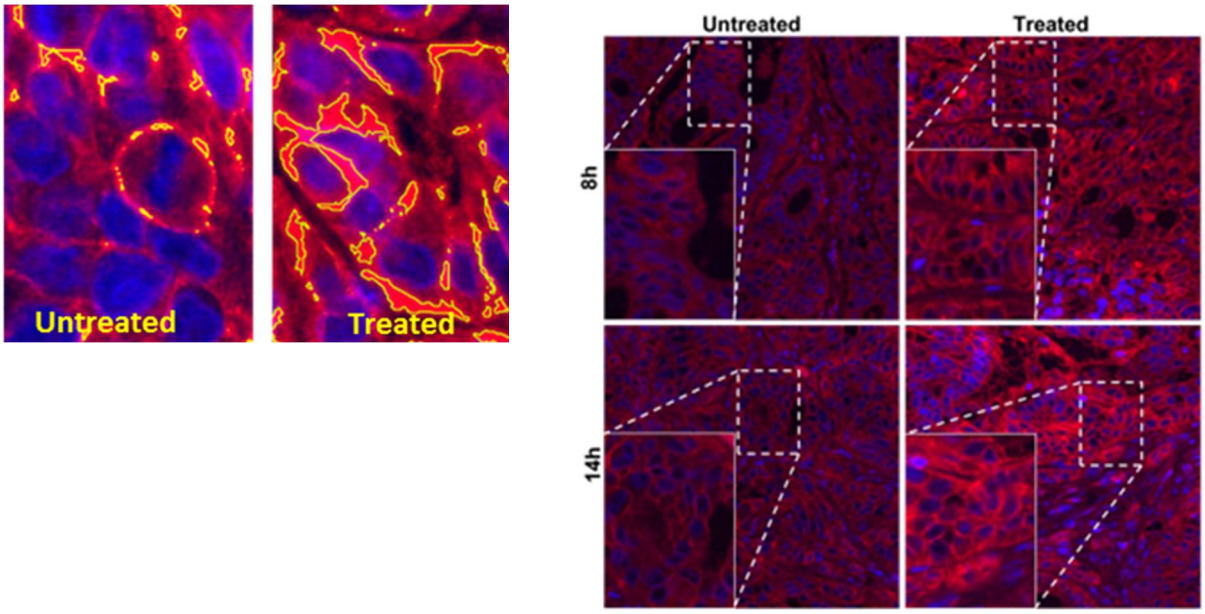


Fig. 37. TRAIL R2 (DR5) death receptor membrane expression [83]

The mitochondrial membrane pore forming and release of cytochrome C (the point of no return to apoptosis) is measured in the treated mice, Fig. 38.

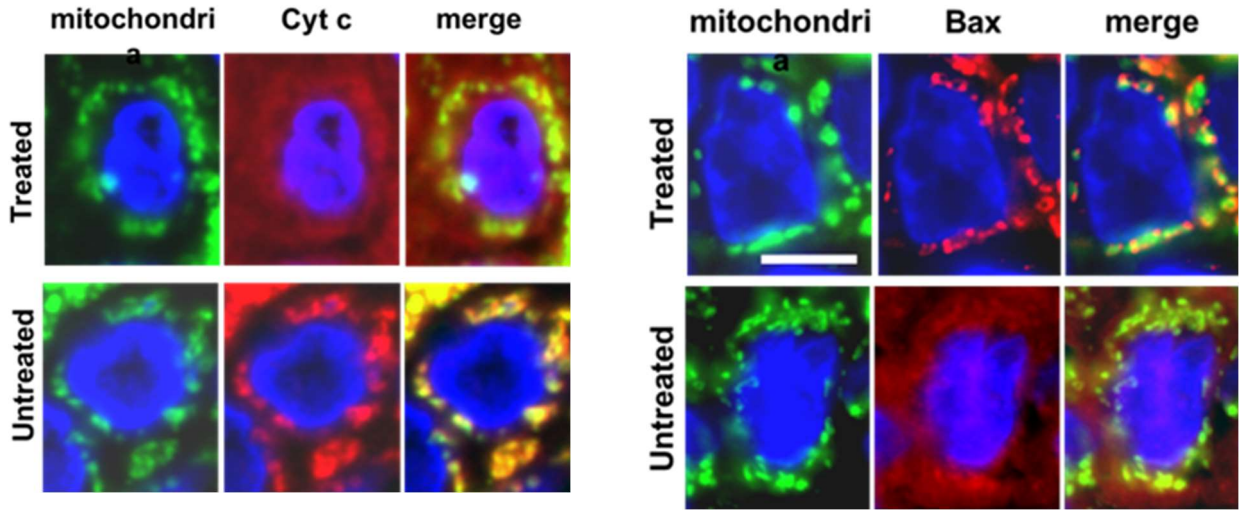


Fig. 38. Bax and Cytochrome C expression on the mitochondrial membrane

The upregulation of calreticulin was typical in the experiments, Fig. 39.

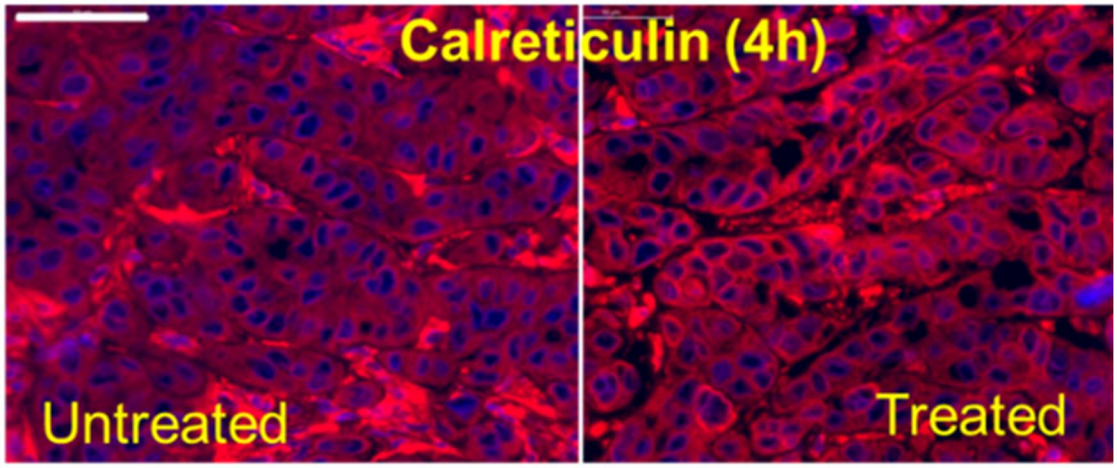


Fig. 39. Calreticulin upregulation at the membrane [83]

Furthermore, many membrane-associated proteins were measured by immunohistochemistry (like FADD, FAS), reporting the energy excitation on the selected membranes.

Because of the massive production of apoptotic bodies, a damage- associated molecular pattern (DAMP) forms, and possible immunogenic cell death ensues. The special molecular interactions allow a bystander effect and possible abscopal effect and probably could lead us to "tumour vaccination" by oncothermia. [89]. These are important for the natural approach to treatment.

Summarizing the in vivo experimental models (immunocompetent and immune-deficient murine models), we used inoculated tumours and metastases in animals. The veterinary cases showed the same effects on naturally developed tumours in animal (preclinical) measurements. Furthermore, the deep penetration and the temperature development are also shown clearly in the animal models.

Veterinary applications

The veterinary applications are real preclinical works, containing naturally developed solid tumours instead of the artificially injected ones in small laboratory animal models (mainly murine models). The results of veterinary cases (treatments are performed in veterinary clinics in Hungary and in Japan), have been presented at various conferences worldwide.

- Published results show the possibility of heating up larger animals (pigs) with 100-150 W in the targeted area [81], [87],
- Cases showing special effects on various tumours, spectacularly improving the quality of life (QoL) of companion animals [87]

Extended preclinical (veterinary) studies were conducted for oncothermia approval, [88], [89], [90], where the temperature was measured in vivo for preclinical use. The first measurements were performed on healthy beagle research animals. Fig. 40.

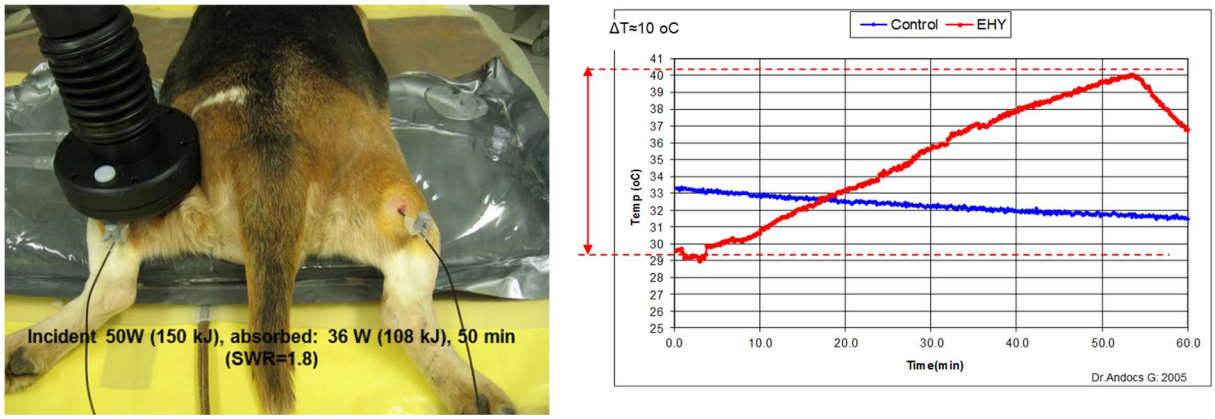


Fig. 40. A beagle dog shows a 10 ºC temperature increase by oncothermia (50 W, 50 min)

The flexible electrodes were well applicable on the curvatures of the animal forms, Fig. 41.

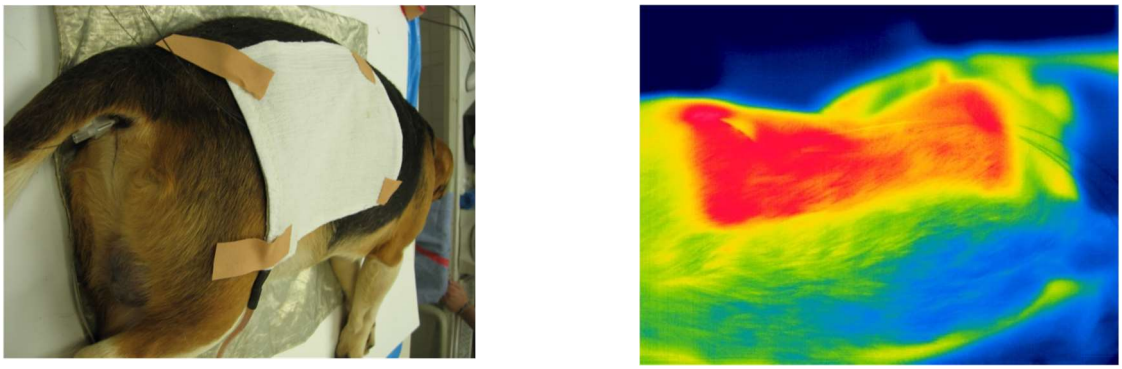


Fig. 41. The thermo-camera spot shows well the definite heating possibility. The electrode was rectangular to show that its shape conforms with the heating.

Later, real tumorous dog patients were measured. Treatment of a 10-year-old male dog with very aggressive proliferative, possible metastases in the regional lymph nodes and fibrosarcoma in the mandibula (left side) was performed [90]. The case is a relapse after surgery and gamma irradiation, Fig. 42.

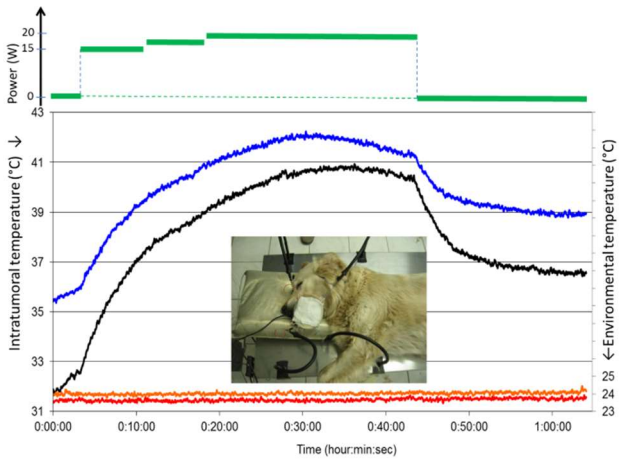


Fig. 42. The temperature rises to 41–42 ºC in the tumour when up to 20 W of power is applied. The treatment had a duration of 45 min.

A 12-year-old old bull terrier shows more than 42 ºC in its tumour [91]. Fig. 43.

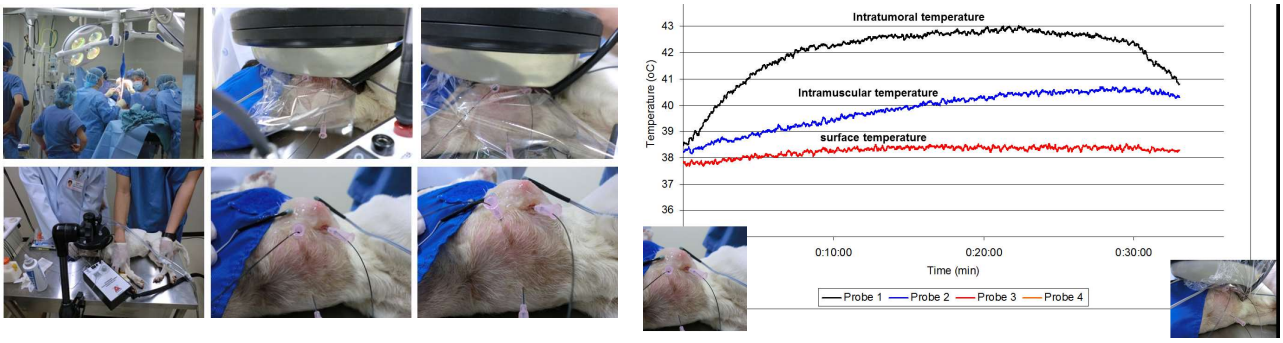


Fig. 43. The intratumoral sensor shows a high temperature in the tumour

Special, high precision temperature measurement was performed recently in the livers of healthy pigs [92]. Fig. 44.

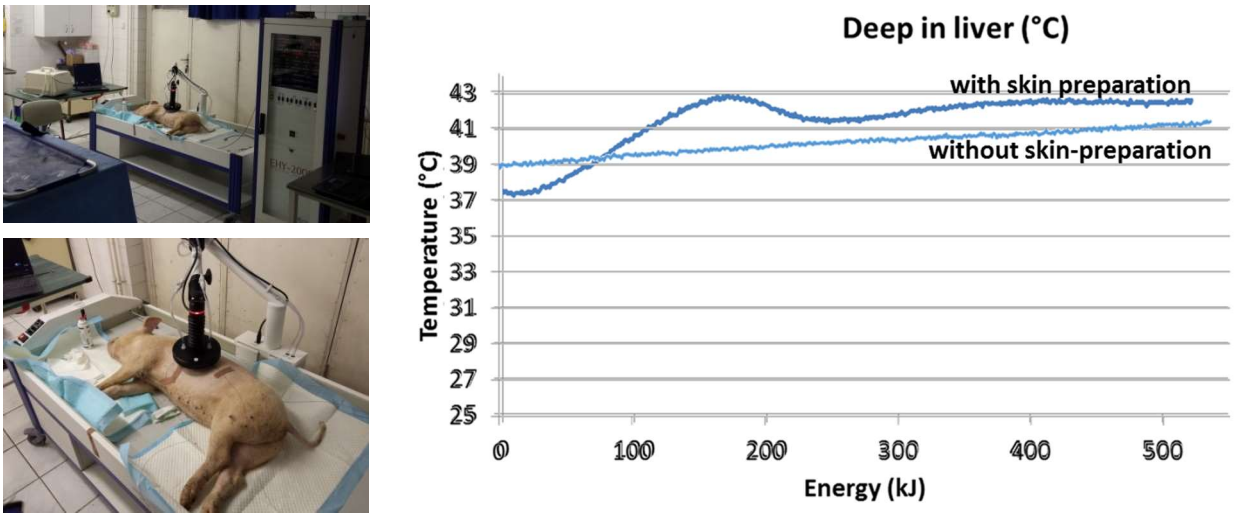


Fig. 44. 150 W, 60 min. (the power was one time down-regulated when the surface was over 41°C) [92]

The veterinary (companion animals and livestock) studies show well the large-body heating facility and the well-functioning bolus system, and the results demonstrate well the animals' increased QoL. These results are intensively used in human studies.

Human clinical studies

- Case studies show that temperatures of 42 °C can be reached deep inside the body, even at lower power [73], [93].
- Side effects are very low with the OncoTherm type of hyperthermia [94], [95], [96].
- The OncoTherm type of hyperthermia can increase survival time and QoL in conjunction with standard therapies [97], [98].
- Even temperature-sensitive parts such as the brain can be treated with the OncoTherm type of hyperthermia [99], [100], [101], [102].

- Clinical efficacy is proven high [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136].

Clinically, it has been shown that the temperature increases in the complete tumour and that blood-flow increase is important for promoting drug delivery to the target. An important prospective double-arm study was conducted with Nefopam in healthy volunteers [137]. (Note: the blood-flow increase and the temperature were directly measured in cervical cancer, presented in the annual conference of Society of thermal medicine, [138].)

Oncothermia treatment is simple and easy to use. Fig. 45.

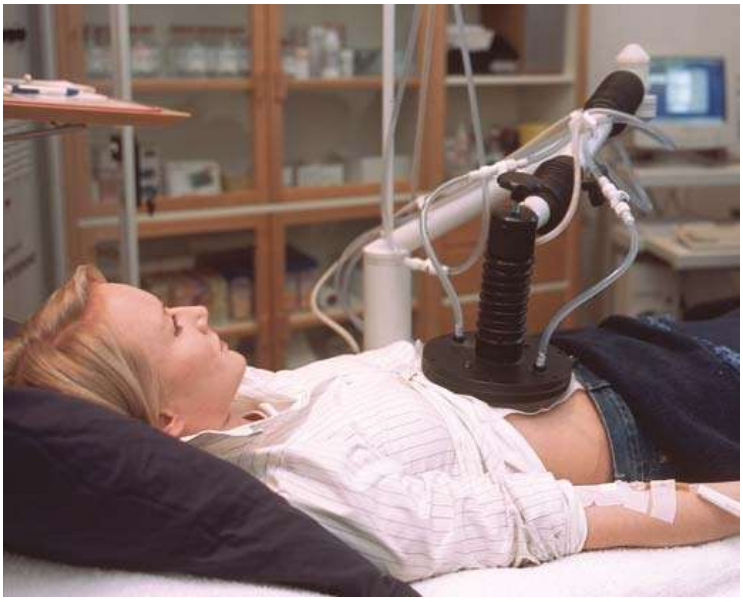


Fig. 45. Oncothermia treatment in clinical conditions

The first and most spectacular indication of the temperature is the thermocamera measurement. Fig. 46.

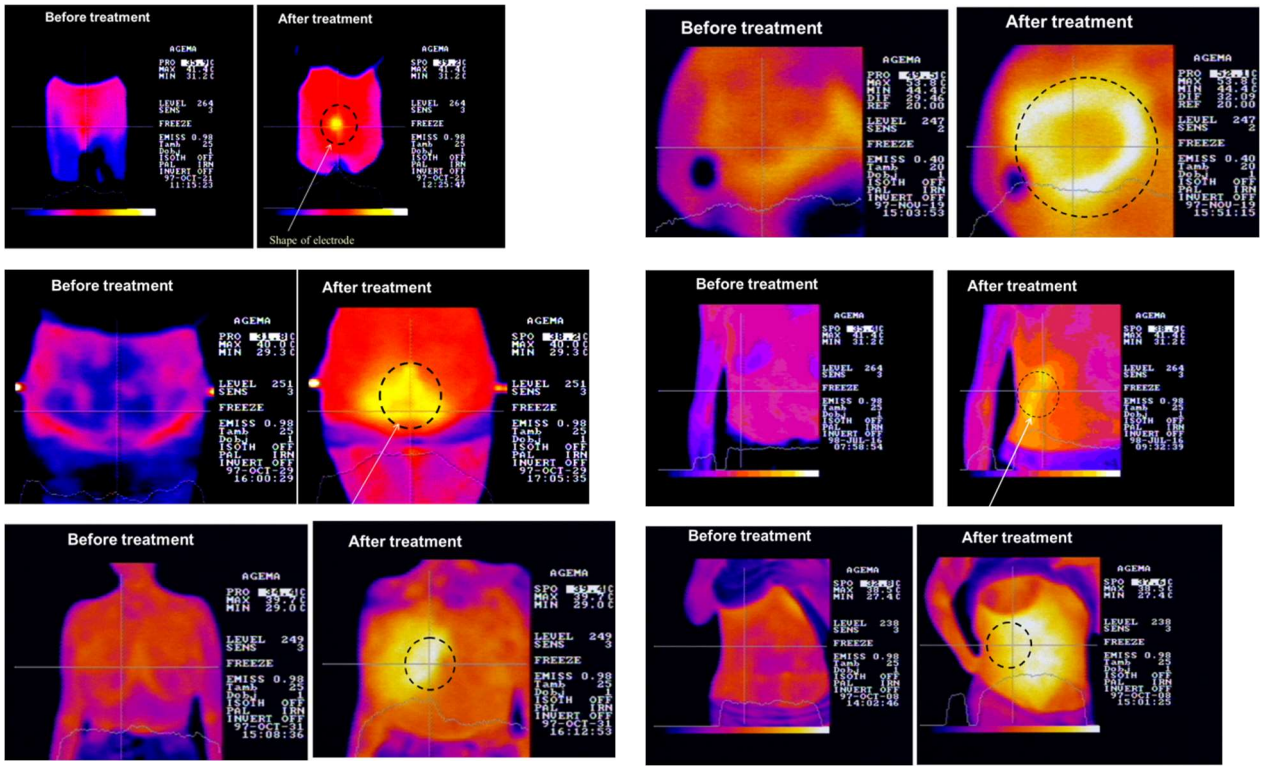


Fig. 46. Various patients before and after oncothermia measured with precise thermos-camera AGEMA-Pro

Temperature measurement of lymph node metastasis of the left side of the neck of a 50-year-old male patient (139). The primary tumour is carcinoma unknown primary (CUP). Squamous cell carcinoma G3 was slightly differentiated. Complex therapy was applied, consisting of trimodal, curative radio-chemo-thermo treatment. Intratumoral in situ temperature measurement (Luxtron fluoro-optical system) applied step-up heating from 50 to 80 W. Low power was used for chemo-induction, inducing mild hyperthermia, a 1.6 °C increase in temperature Fig. 47.

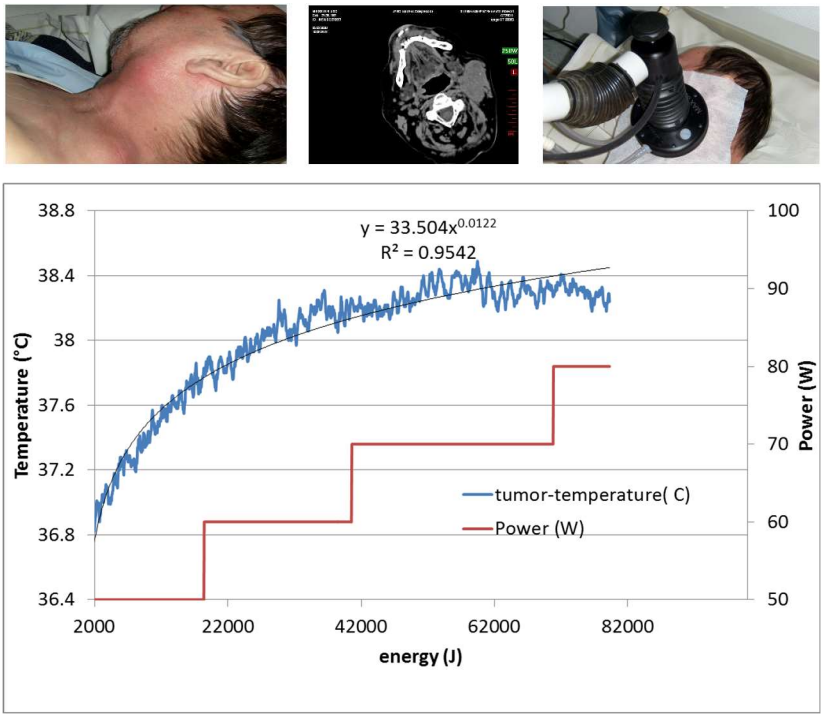


Fig. 47. Temperature development in lymph node metastasis. Low energy was used, causing mild hyperthermia.

Another male patient (87-year-old), with malignant fibrotic histiocytoma G3, was treated with curative radio-thermo therapy (double modality), and oncothermia was used to measure intratumoral temperature in situ [31], which was greater than 43 ºC in the tumour. Fig. 48.

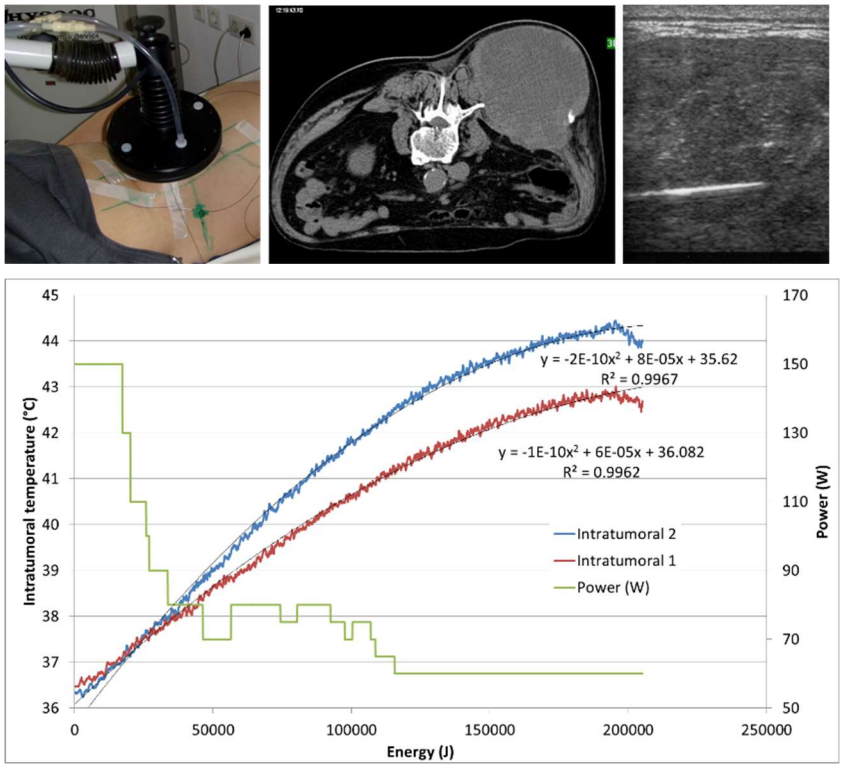


Fig. 48. Sarcoma lesion, huge tumour. The temperature could be raised high enough (>42 ºC), even by low energy application (<100 W on average).

Treatment of ovary was also registered [140]. Fig. 49.

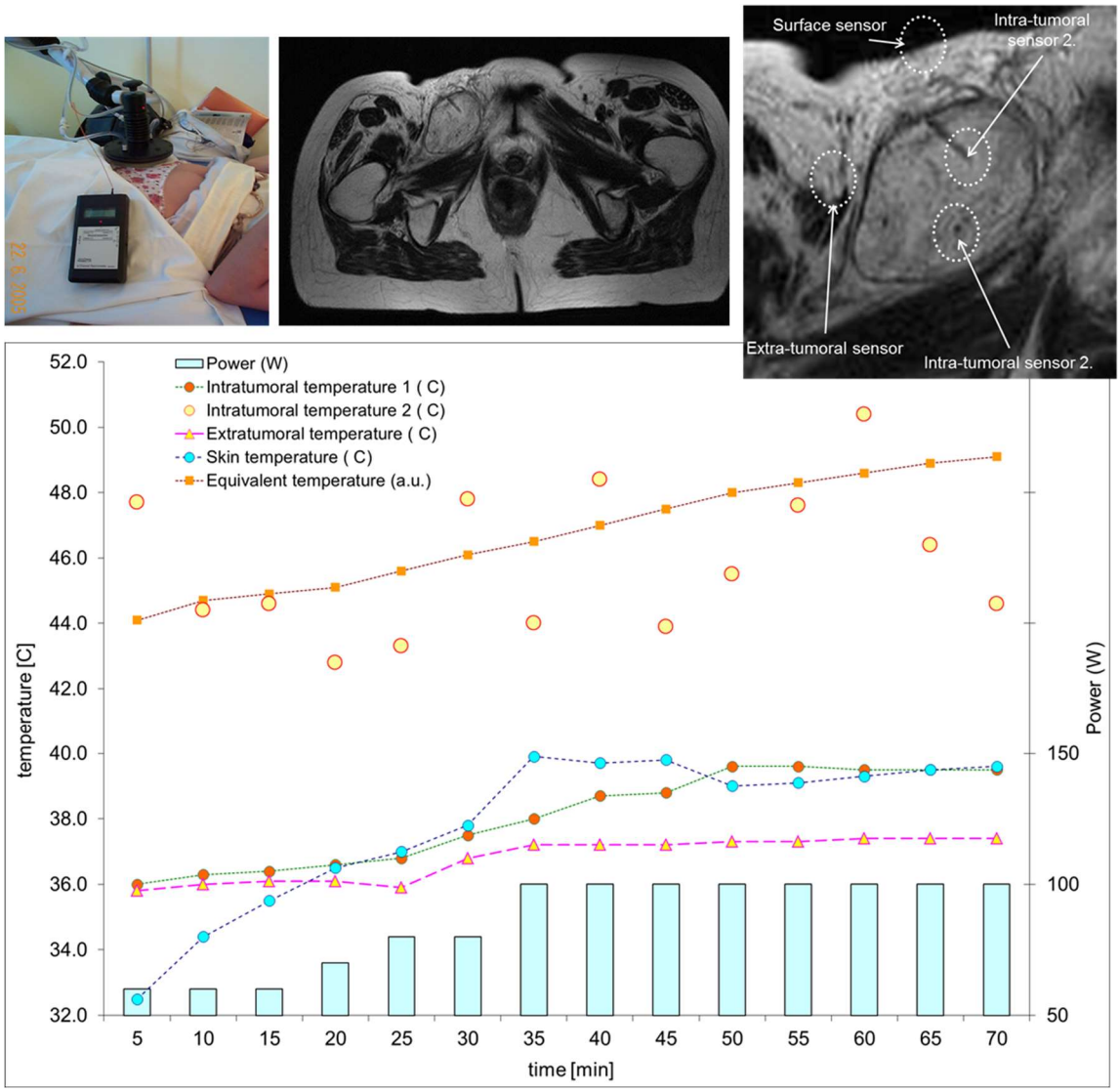


Fig. 49. Treatment of ovary. The maximal power was 100 W, while the temperature was measured very heterogeneously. One part of the tumour was heated extremely (probably it had necrotic volume where the sensor was inserted), whereas the other part had mild hyperthermia over 39 ºC.

Temperature measurement in the abdomen (12 cm in depth) was also measured by interventional radiology positioning [140]. The measured temperature was over 41 ºC, with maximal power of 140 W. Fig. 50.

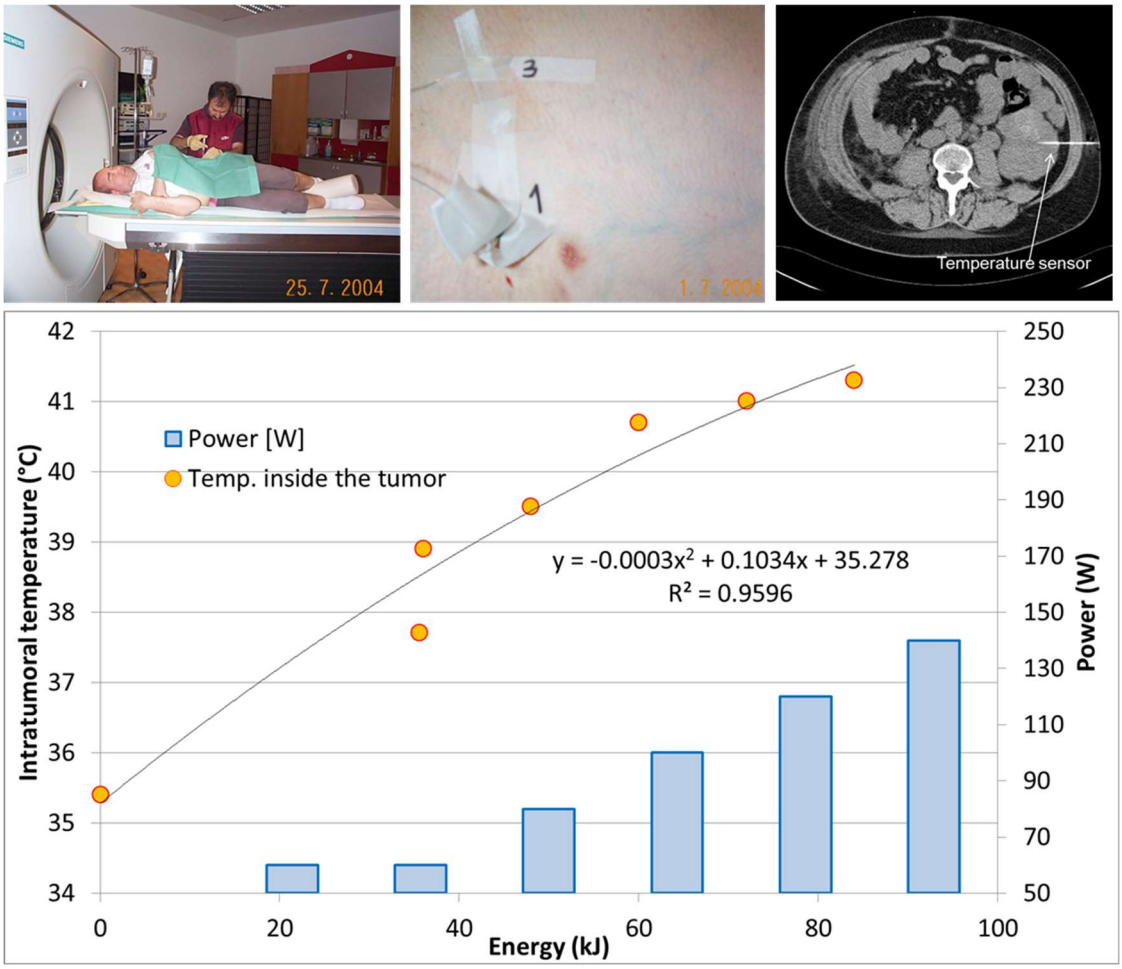


Fig. 50. Abdominal temperature measurement

Temperature measurement of mammary carcinoma shows elevation of the temperature by 140 W over 41 ºC (140). Fig. 51.

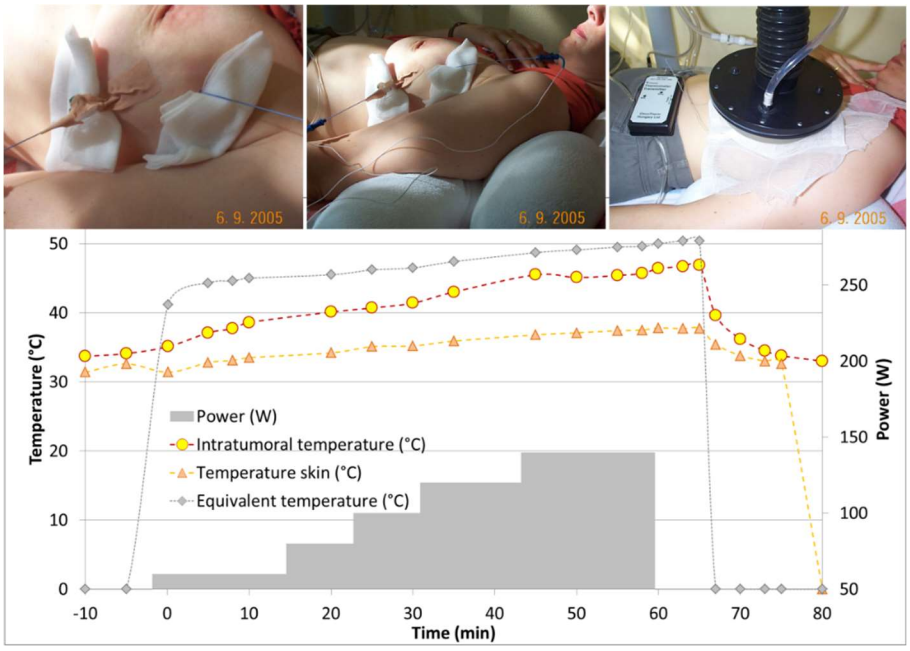


Fig. 51. The temperature of mammary carcinoma closely follows the equivalent temperature, due to the fatty tissue dominance in the breast.

Abdominal treatment with two intratumoral sensors shows high temperature at 150 W end power [140]. Fig. 52.

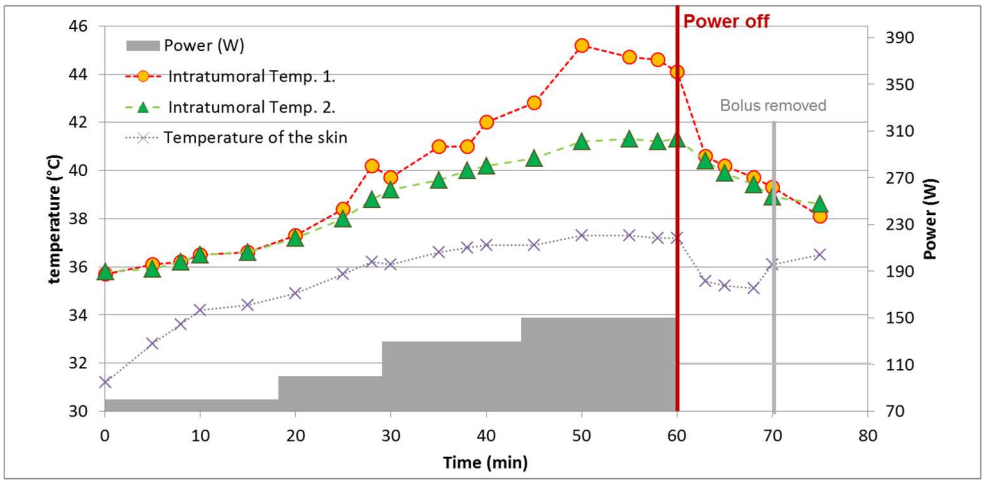


Fig. 52. Intratumoral sensors in cancer of abdomen location.

Oncothermia treatment of the abdomen also shows increase of the temperature, Fig. 53.

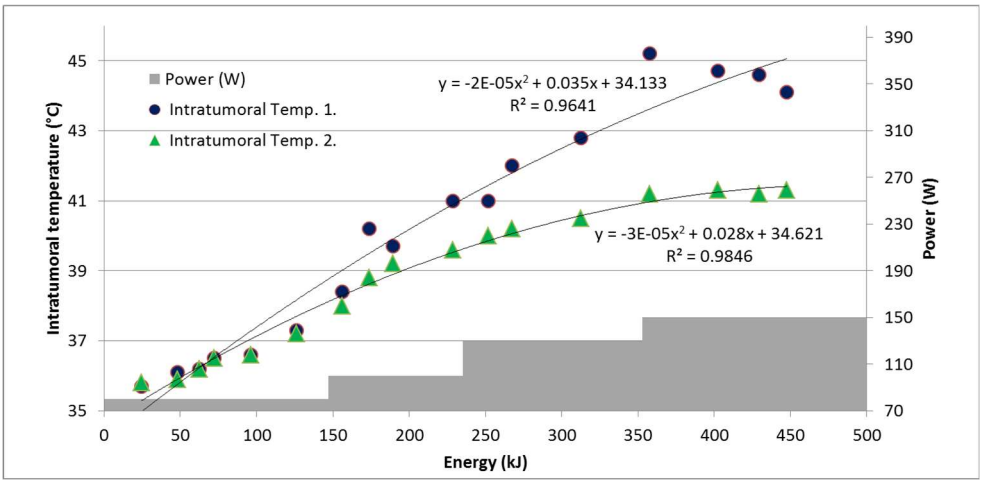


Fig. 53. Time dependence and energy dependence of the temperature development in abdominal treatment

Invasive temperature measurement in the cervix uteri shows high temperature with low power supply due to the low blood perfusion into the area [141]. Fig. 54.

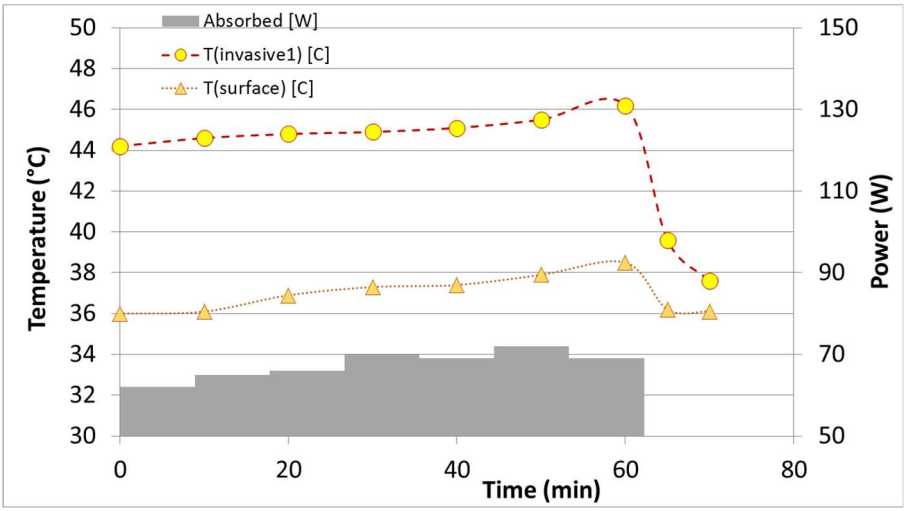


Fig. 54. Cervix temperature is shown high, while the surface temperature increases moderately

Several effects could be shown at all research levels. These consist of the basics of hyperthermia (heating) and those of the Hippocratic oath (nil nocere – do no harm). Every research level interacts with others, and their feedback and learning are effectively used under various conditions in complex oncothermia research.

This nano-targeting makes personalized, precise and controlled clinical treatments possible. The clinical success well proves the special character of this method, [142], [26], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156].

Discussion

Heating

One of the basic principles of hyperthermia is that the tumour can be heated up, depending on the definition, either to normal body temperature or to another specific temperature. A temperature increase to 42 °C can be demonstrated in in silico, in vitro and in vivo models, as well as it was proven in both animal and human measurements.

OncoTherm devices are capable of heating up even larger, deep-seated tumours inside the body using the "low" power of capacitive coupled RF power.

Side effects (toxicity)

To date, the only known side effects discovered in any model when treatment protocols have been followed are first-degree burns (skin-redness, <8% of cases) and second-degree burns (blisters, <3% of cases).

Focusing

In silico and in vitro models of oncothermia have shown 100% tumour-cell specificity. At higher levels, proving the theory is more difficult, but no contradictory results have been obtained. However, we should consider that the OncoTherm type of hyperthermia can be applied to brain tumours, for which conventional hyperthermia is contraindicated. This is because heating normal cells and tissues

will generate a protective mechanism in the brain, which causes oedema. However, this type of reaction was not found with the OncoTherm type of hyperthermia.

Special patients: Non-heatable patients

In conventional hyperthermia, the "non-heatable" patient group consists of patients in whom the tumour (average) temperature cannot be heated up to more than 40–41 °C. By using the OncoTherm method (part of) this group can still be considered heatable, as the cell membrane temperature can be 3–6 °C higher than that of the cell or its surroundings. This means having a temperature of 36–39 °C, as an average temperature could already generate a temperature of 42 °C in the cell membrane, producing a hyperthermic effect (effectivity), as in conventional hyperthermia.

Future

For the immunological effects, the immune system must be prepared for the fight against cancer; the adaptive immune system must make preventive steps to demolish the tumour. This immune-effect is only possible if the immune system is not heated above 40 °C, otherwise the therapy is not only against the tumour cells but against the immune cells, too [157], [158]. Due to this it could be a big question to check the best temperature for the treatment (like by whole body hyperthermia now we known that the moderate (38-40 °C range) is better than the extreme (42-43 °C) one). Oncothermia is a mild-hyperthermia in the tumour tissue but extremely large in cancer-cells at cellular locations [159], [160].

These facts are extremely important in integrative medicine, where the immune effects are crucial. For this reason, the results of [161] were particularly encouraging. They used immune stimulators and achieved long survival times. We applied the TCM immune-stimulator (Xiao-Aiping) in laboratory animals (murine model) and obtained a fantastic abscopal effect, supporting the earlier clinical results of Gurdev et al.

Conclusion

Temperature development by the oncothermia method is shown in all research and study lines: in silico, in vitro, in vivo, preclinical (animal) and human studies. The temperature corresponds to mild hyperthermia (increasing the local target volume) temperature by more than 3 ºC, while nano-heating of membrane rafts produces local extremes of additional 3 ºC increases over the target volume average.

Oncothermia has definite clinical advantages:

- High efficacy and safety issues. Efficacy is increased by apoptosis induced by selective heating. We observed that these natural nanoparticles are transmembrane proteins, containing the most important signalling networks for apoptosis.
- We have shown that apoptosis exists and constitutes a special kind of cell death: immunogenic cell death. (These are published in high impact factor, peer-reviewed Journals [162], [163].) This induces the immune effects and causes an abscopal effect in the body. Clinically, this results in a higher QoL of the patient.
- The selected tumour cells need much less energy to heat up than the complete cancer tissue. Consequently, oncothermia needs less incident power than other conventional hyperthermia devices, which makes surface burns rare.

- Furthermore, due to the low incident power, there is a low risk of burn, despite of the moderate cooling of the skin. Due to the low cooling loss, the incident power is mainly absorbed in the target and makes setting the dose of the process according to incident energy instead of the temperature rise possible.

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