The Oncotherm story in personal view (History of modulated electro-hyperthermia)

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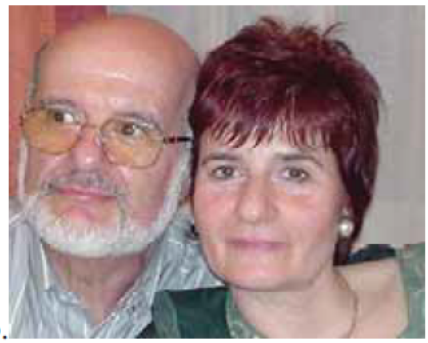
Introduction

Introductory personal notes

My mother died of cancer… She was young... She suffered horribly… She could not see me graduate.….

Many years afterwards, my sister was diagnosed with the same type of cancer … The prognosis was very bad…
In the time of my sister's illness oncothermia was already in use. My sister was rescued. She lives happily…

a.  b. 

I am with my mother, in my childhood (a); and with my sister, now (b).

My family understood my new directions, and supported me as much as they could. My wife and my two children chose this topic as well. My wife, Dr. Susan Szasz-Csih helps in organizing, my son, Dr. Oliver Szasz leads the OncoTherm Group, and my daughter, Dr. Nora Szasz is active in bio-engineering science.

Company's history in nutshell

I graduated from Science University, as a Physicist in direction of solid state physics (material science), in Budapest. I started first with theoretical physics (statistical physics) working on the Ising-model for phase transitions. My interest, Later I started to focus on the instabilities and metastabilities of electronic structure of materials near their phase-transitions.
From the beginning, the metastable, instable materials, phase transitions and their electronic structure were in the centre of my interest. Most of the instabilities were studied on the surface-processes (catalysis, corrosion, layer-growth, wear- and absorption-processes, coating structures, etc.) I was more and more interested in the practical applications of my knowledge. I developed many practical coating structures, mainly amorphous metal-layers with extreme corrosion- and wear-resistance (Metamorf© coatings).

The logo and info-sheet of Metamorf© coatings

I made numerous patents for the practical use of Matamorf© on various substrates (metals, semiconductors, isolators), with the ability to be applied on a wide range of structural surfaces (porous, textile, tubes, etc.) and hard composite materials with diamond and boron-nitride. I had a special department at the science university (Laboratory of Surface and Interface Physics), working together with many talented young scientists, leading MSc- and PhD-theses, teaching physics in point of view of complexity. I established the MetaLab© Interdisciplinary Department of the Science University Budapest in 1983, as a very new concept of interdisciplinary Laboratory.

A part of the brochure of MetaLab© Interdisciplinary Department in Eotvos Science University, Budapest

I started searching for international connections with similar surface laboratories. I built up good cooperation with the Surface Laboratory of Zhdanov University, St. Petersburg (from 1980) and with the Scottish Surface Center, Strathclyde University, Glasgow (UK) (from 1984). I was appointed visiting fellow in Glasgow (1986/87) and afterwards appointed visiting professor for the next 17 years.

My attention was focused on high-temperature superconductor ceramics from 1986. These materials are highly instable, having many specialties of their local stability, so the knowledge which had been collected for years before, was well applicable for these new kinds of material. The knowledge was amazing, and soon its applicability in biology became obvious. My interest turned to biophysical effects at the cellular membranes and physiological feedback mechanisms to make stability of these instable systems. Especially the tumor-medicine attracted my attention. When it became trivial that I am able to do something in this line, I did not hesitate: I completely changed my scientific direction, concentrating only on the tumor-biophysics. Parallel with this a serious decision was made: I decided to establish a special company for development, to concentrate on the treatment techniques. This was the time of the establishment of Oncotherm in 1988. This university spin-off was one of the firsts of the limited companies in Hungary, established under the law of 1930, due to missing regulation of such kind of private enterprises in the socialism. The name was “Surface Technics Ltd” later Inter-Rest (Interdisciplinary Research and Trade) Ltd, and later had its final name Oncotherm. Meantime, the applications were centered to a German private clinic (Clinic St.Georg), where Prof.Dr.Douwes was my research partner and applied my technical developments in medicine. The full medical process was worked out in Germany, and the approvals were German granted in 1994 by the largest Notified Body for quality assurance of medical devices in Germany: TUV-Sued, Munich. In the same year we established a German company, Medicos (later OncoTherm) in Bavaria together with Prof. Douwes.

Logo of InterRest Medicos Ltd.

Due to Prof. Douwes' medical duties, he did not concentrate on market issues, so we split in 1998, keeping the tight and fruitful contacts of common work. After this, due to unfortunate problems, the German company started to be dissolved in 1999 (the Hungarian Oncotherm was intact in this process). Soon a venture capitalist company (HighTech, Dusseldorf) helped to renew the German business in 2001. We established the HOT-Oncotherm company in Troisdorf, as the marketing arm of the Hungarian Oncotherm (which was led by my son, Dr. Oliver Szasz). HOT-Oncotherm is specialized in trade and keeping the full German approvals in medical method and technology. At the end of insolvency process of Oncotherm in Bavaria, HOT-Oncotherm bought the name, and since 2005 it has had the same name as its Hungarian partner, Oncotherm again.

Logo of HOT-Oncotherm and Oncotherm Ltd

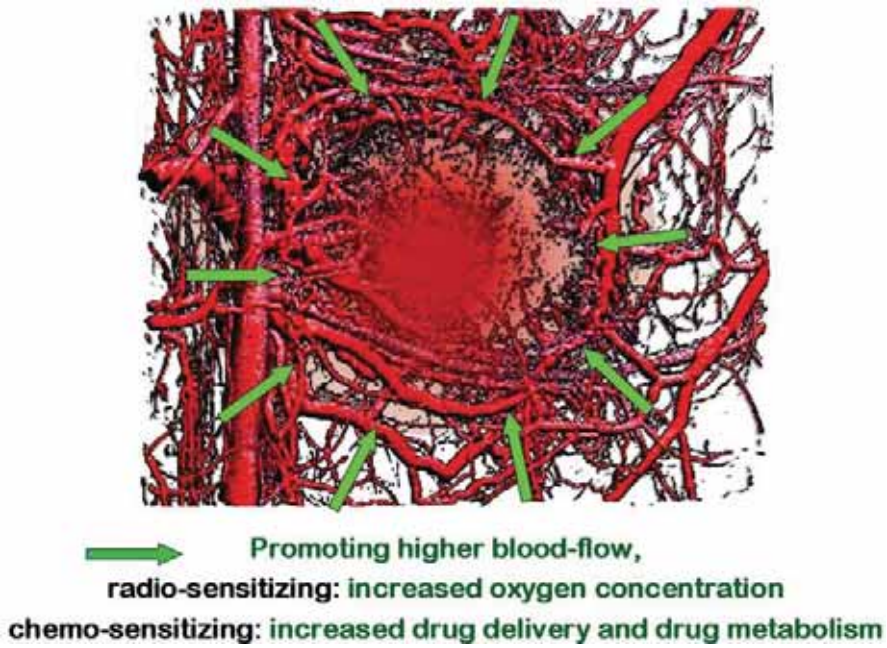
Temporarily, as interim solution, I took over the CEO position in German Company in 2008 (while my son remained the CEO of the Hungarian one). The two companies received a common quality assurance from TUV-Munich, and in 2010 I took over the CEO position for my son in the Oncotherm Group, (which contains both the OncoThem Companies in Germany and in Hungary). We established a strategic partnership for high-tech production with Tateyama Machines Ltd. (Japan) in 2011, to serve our customers and their patients with medical method by standard of Germany and the electronic production by Japanese standards. The Hungarian company remained as it was; it is the basis of research & development processes of oncothermia, and I am serving as Chief Scientific Officer (CSO) in OncoTherm Group. I am proud to be a developer of this method, representing the high quality of biological knowledge in Europe which is based on the famous German approach of medicine (MED in Germany).
Oncothermia has formulated a new paradigm: [1], and has made it clear: "What is against the acceptance of hyperthermia?" [2]. The problem is the misleading aim getting uncontrollable temperature as dose and the ignorance of the physiological reaction of the patients. The oncothermia solution provides a positive solution to the doubt and introduces the fourth column of the gold-standard oncological methods, additional to the surgery, radio- and chemo-therapies.

Oncothermia – further development of hyperthermia

Oncothermia is a further development of hyperthermia in oncology [3]. It is a modern hyperthermia, keeps all the advantages of the classical hyperthermic oncology and avoids the disadvantages, makes the process controlled and repeatable.

Hyperthermia in oncology

Hyperthermia in oncology has a long history but low acceptance among the oncology professionals. The main, classical effect of hyperthermia is to increase the blood-flow in the target volume (tumor), and so sensitize it for radiotherapy (by delivering high oxygen concentration) and for chemotherapy (by increased drug delivery and higher drug metabolism.



Sensitizing effects by blood-flow stimuli of local hyperthermia

Incredible number of papers has been published in silico, in vitro and in vivo research as well as on the clinical applications. Numerous clinical studies have proven the efficacy of hyperthermia and many books have been published on the results ([4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22]). It is a perfect technology in principle. What is the problem then?

What is the problem with hyperthermia in oncology?

Hyperthermia has numerous impressive results in clinical trials, published in the books and professional publications. However, the results are sometimes very promising and significantly show the healing power of hyperthermia, but there are disappointing clinical trials as well. The real challenges are of course the controversial results, addressing many further questions and raise doubts.

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 [23]. 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" [24].

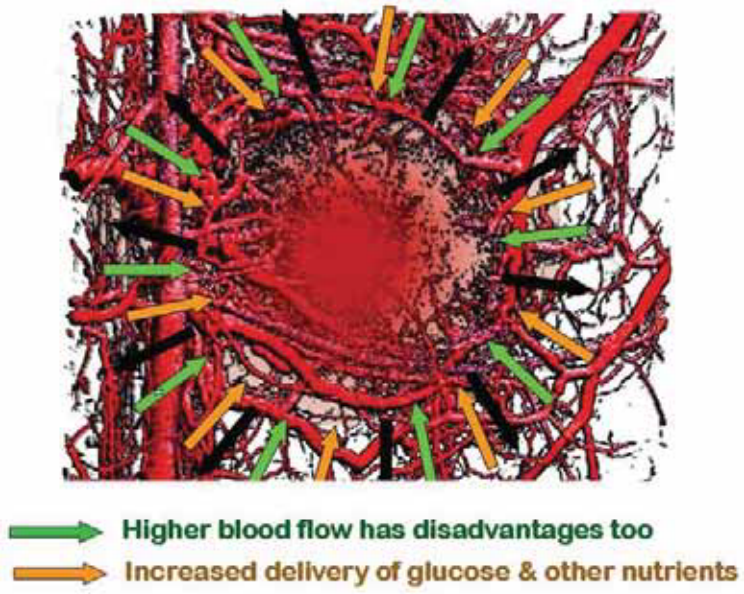
The present situation apparently supports the above opinions. The relevant literature formulates numerous questions even in the titles [25], [26], [27], [28], [29], [30], [31], [32], [33]. One of the earliest questioned the readiness of the radiotherapists: Is the community of radiation oncologists ready for clinical hyperthermia? [34]. The main points clearly formulatedthe problems: "Clinical hyperthermia today is a time-consuming procedure, done with relatively crude tools, and it is an inexact treatment method that has many inherent technical problems. Certainly, excellent research work can be working in the community. If the individual is willing to sacrifice the time and effort required to participate in clinical studies in this interesting, challenging, exasperating, not-too scientific field; then he or she should be encouraged to do so. The field is not without its risks and disappointments, but many cancer patients with recurrent or advanced cancers that are refractory to standard methods of medical care can unquestionably be helped by hyperthermia. It is not, as some have suggested, the fourth *major* method of treating cancer after surgery, radiation and

chemotherapy. It may be innovative, but it is still an experimental form of therapy about which we have much to learn."

Dr. Storm a recognised specialist of the hyperthermia formulated a very negative opinion about hyperthermia in his paper: What happened to hyperthermia and what is its current status in cancer treatment? [35]. He wrote: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment."

Two editorials dealt with the questioning of hyperthermia in oncology. One in the European Journal of Cancer in 2001: A future for hyperthermia in cancer treatment? **[23]**. It formulated: "The role of hyperthermia in oncology cannot be defined at this moment. Obviously it will be limited to specific scenarios,… ." The other editorial was published in the Annals of Surgical Oncology (titled: Hyperthermia: has its time come?) in 2003 [36] formulating: "The results of adjuvant intrapleural chemotherapy for mesothelioma with or without hyperthermia have been less than hoped for." However, both editorials expect new clinical results and new, more effective hyperthermia techniologies.

Demand for change of paradigm of hyperthermia in oncology is matured. One of the flagship clinical study of hyperthermic oncology was published about cervical cancer, where the results were very promising [37], but the control study was disappointing [38]. The explanation may be simple: a reference point was missing, [39]. The missing reference is due to the simple thermodynamic fact: the temperature cannot be kept locally in a spot, it is smeared automatically. The temperature by its way tends to be equalized; the focus is extended by time, due to the very effective heat-exchanger the blood-stream. The amount of the energy loss deviate by the actual conditions, and by the fundamental law of nature, the temperature smears in the environment. Any proper focus serves as a heat-source to heat up its surroundings.



Unwanted effects of temperature: delivery of nutrients to supply the tumor and disseminations of the malignant cells are more likely

The heated tumor strongly exchanges its heat with its healthy surrounding, extending the focus gradually and increasing the local blood-flow. The intensive blood-flow has the risk of the further disseminations, and metastases, so the classical hyperthermia could support the metastases, [40], [41], [42]. Furthermore, the blood-flow is increased locally, supplying the tumor with nutrients (first of all with glucose) and the higher temperature gains the local metabolic rate as well. There were also reports about the induced hepatitis by hyperthermia [43].

It is clear, that the absolute proper focus, having microscopically fit in the contour of the tumor is a kind of surgery, treating (cutting) the tumor-lesion. However, the malignancy is not a local disease by its definition, it has a danger of dissemination, which cannot be treated locally. The treatment

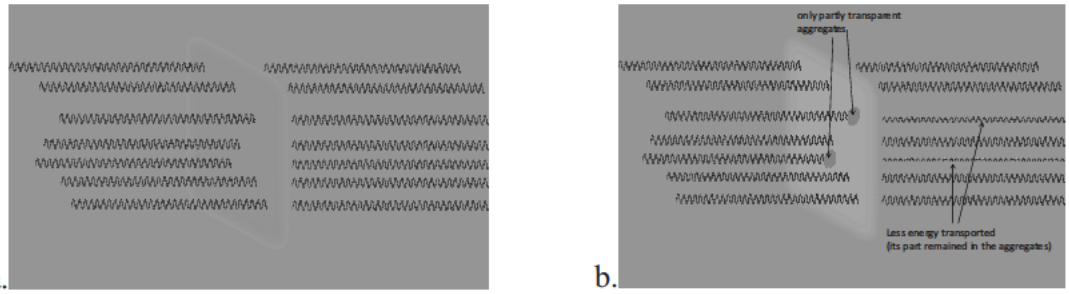
has to select on cellular level between the malignant and healthy cells, and even find every single cell carrying malignancy.
The temperature and energy distribution are very different in the body [44]. It is not possible to fit the specific absorption rate (SAR) and the developed temperature, because the effective heat-exchanger, the blood-flow can cool down the high-SAR target, while the part of the target with low blood-flow will have a high tempretaure due to a low SAR value.
These challenges are definitely complex, and can make the actual hyperthermia treatment uncontrolled. This branch of consequent problems could be the reason for the controversial results and the weak acceptance of the conventional hyperthermia.
The challenging issue has always been technical: how to heat in depth, locally focused, selective of malignant cells, and on the other side: how to control it and how to measure the efficacy of the treatment?
A typical capacitive coupling solution pumps enormous energy, exceeding 1 kW. The rise of temperature after 45 min was 4.8 ^{o}C but the reached focus did not differ greatly in its temperature from its overall neighborhood [45]. The focus, however, was not effective. The temperature was distributed by time. In case of radiative applications the situation was not better. The temperature elevation in the tumor after 57 min was 4.2 ^{o}C; reached by as high power as 1300 W, [46]. The overall heating is obviously shown with some characteristic (unwanted) hot-spots. The elapsed time smeared the relative focused temperature. The temperature increase in the tumor was in average 4.2 ^{o}C, while in the surrounding muscle it was 3.8 ^{o}C **[46]**. Is this the focus, which we expected? The few centigrade increase of the temperature by 1300 W energy shows how much mass is heated instead to concentrate on the tumor. To see the power capacity, we compare the electric heating for tea-making. A standard speedy Electric Tea Kettle uses 1500 W to boil two cups of water within two minutes. The increase of the temperature for the ~ 0.5 liter water is ~75 ºC. The electric power can change temperature effectively when it is used to do so.. The electromagnetic radiation increases the tumor temperature by 3.2 ºC, while the intensively cooled, large volume water-bolus had a higher increase (5.8 ºC) with pretty linear growth slope **[46]**.

How oncothermia chages the paradigm?

Oncothermia changes the paradigm. Oncothermia technology heats non-equally; concentrating the absorbed energy to the intercellular electrolytes **[3]**. This method creates inhomogeneous heating, microscopic temperature greatly differs 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. The synergy of electric field with the thermal effects potently and selectively does the job [47].
An electric field application without an increase in temperature (using less than 5W power) has also been found effective against cancer [48], [49], [50], [51], [52], [53], by using galvanic (DC) current applications. The control of these treatments is the tissue-resistance and the quality parameter is the applied charge load, [54], [55]. Numerous devices were developed and applied widely, but the expected breakthrough result was missing. An entirely new line was started with Professors Rudolf Pekar, [56], [57], [58], Bjorn Nordenstrom **[52], [53]** and Xin You Ling [59], [60], [61]; and continued by others [62], [63], [64], [65], [66], [67], [68]. Remarkable results were produced by this method; and the biological mechanisms involved in electromagnetic field were intensively investigated [69], **[1]** and the effect of electric field was studied on various side of its complex behavior, [70], [71].The physiology is interdisciplinary, applies numerous principles and discoveries. The electronic structure approach of solid state physics (e.g. Szent-Gyorgyi, [72], [73]), the superconductivity (e.g. Cope, [74]), the electromagnetism (e.g. Liboff, [75], [76]), the thermodynamics (e.g. Schrodinger, [77], Katchalsky & Curran [78]), etc. are all parts of physiology, and make it really complex as the phenomena of life itself is. The living organism develops itself, rearranges, reorganizes the incoming chemicals and builds up its own structure, consequently lowers the entropy. Various modern approaches were developed in the last decades

on this complexity, like self-organization ([79], [80], [81], [82],), fractal physiology ([83], [84], [85], [86]), and the bioscaling ([87], [88], [89]). Oncothermia uses these new approaches to fit it for the best curative performance. This new approach (the fractal physiology) is applied in oncothermia. The carrier electric field delivers the time-fractal structure to the tissues, considerably enhancing the selection between the connected healthy cellular community and the individual autonomy of the malignant proliferation.
The method is similar to the process when the light goes through the glass. windows When the glass is transparent to that specific set of colors (visible light, definite interval of frequencies) its absorption is almost zero, all energy goes through it. However, when it has some bubbles, grains, precipitations etc. those irregularities will absorb more from the energy, their transparency is locally low, their energy absorption is high, they are heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example.

a. b.



The transparency of the glass. In full transparent case all the energy goes through the glass (a), but when the glass has aggregates , those absorb a part of energy (b), and they will be hotter than their environment

This is the effect, which used in oncothermia with special modulation of the carrier frequency. The carrier frequency delivers the information (modulation frequencies), for what the cancer cells are much less "transparent" than their healthy counterparts are. Malignant cells are heated up by the selectively absorbed energy.
What makes the difference in the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special "social" signals [90] 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 disappeare [91].
There are special biochemical and biophysical changes caused by the above differences of the malignant cells and used for oncothermia specialties:

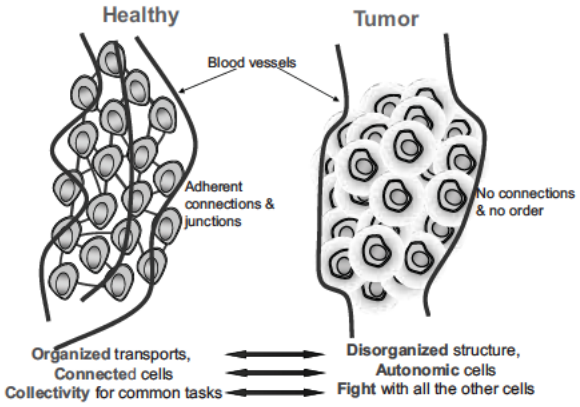
- their extracellular matrix has different concentration of ions [92], which can be measured by positron emission tomography, PET [93];
- they have different conductive behaviors [94] which can be measured by electro-impedance tomography (EIT) [95];
- their electromagnetic environment (how they conduct the electromagnetic currents and waves) is different, [96], [97]. This can be measured by Cole-Cole impedance measurements [98].
- order of their electrolyte (aqueous solution) differs, [99]. The healthy tissue has ordered water-states [100], in extracellular matrix [101], [102], while malignancy decreases the order of the electrolyte matrix, decreasing the cell-cell adhesion promoting the proliferation [103].

- The dynamical process has special self-organization [81], forming special structures [84], [85], bioscaling [87], and noise spectrum [86], which certainly differs in cancerous state. The information to recognize the tissue is well coded in the order of those [79], [80].

The disordered structure of malignancy is a good absorbent. To show it again, there is a simple example: when somebody's hair is in order, the comb slides through the over-combed hair. However, when the same hair is disordered, the combing is able even cutout the hairs by their energy-absorption mechanisms. In malignancy the disorder makes the same energy-absorption process.

Combing puts different energy into the hair depending on its order. (Picture is a part of Renoir's painting)

The healthy cells are ordered, they are in harmonic cooperation, forming a net of connections. Malignant cells are autonom, they are individual "fighters", having disorganized structure. This difference is used by carrier-frequency delivered modulation to select between the healthy and malignant cells.

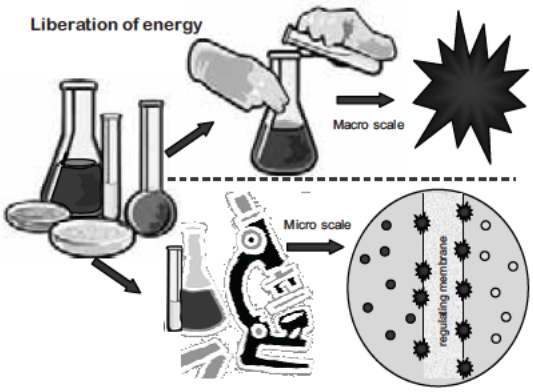


The malignant absorption selects by the disorder of the cancer, having no transparency for the well-chosen modulated RF carrier frequency (It is a patented method and know-how of oncothermia.)

The adequate corrective actions for these challenges would be the more precise targeting, decreasing the loss in the surroundings and avoid the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increase the efficacy:

1. Apply the electric field as carrier of the energy, and that field cannot be compensated by homeostatic control
2. Apply correct microscopic targeting, using the energy-absorption cell-by-cell efficiently.
3. Apply such mechanisms, which initialize natural effects to kill the malignant cells.
4. Apply mechanism, which carries info for disseminated cells to be blocked.

One of the most modern energy sources of our time are the fuel cells. These liberate their energies in small (micro) fractions, regulated by an appropriate membrane.

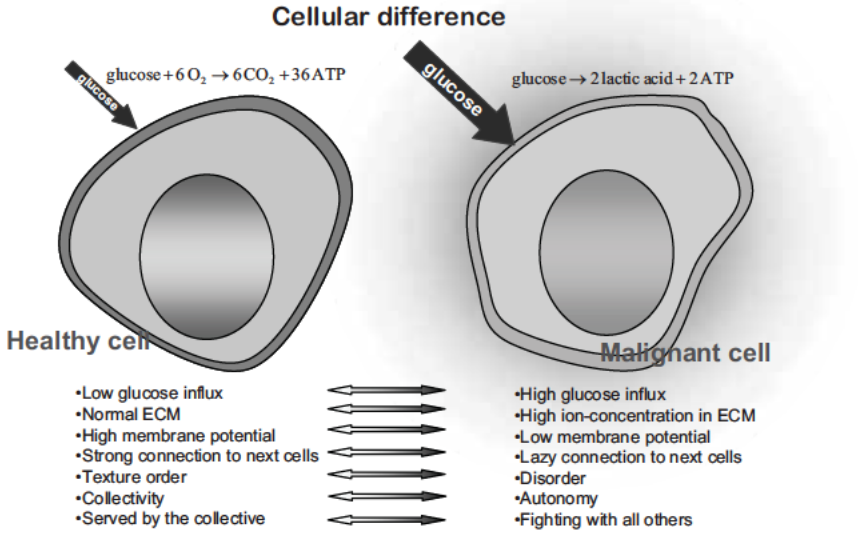


The fuel-cell concept of energy liberation: go microscopic. The same concept is used in life-processes

This energy liberation makes using the energy possible in the most effective way. Besides, the life processes use the same surface controlled energy-liberation, producing energy in small steps in multiple cycles.

The malignant cells are in frequent and permanent cellular-division. Their energy-consumption for the intensive division is definitely higher than the energy request for the healthy cells in homeostasis. A high intensity mass-production of ATP is necessary to fulfill the strong energy-demand. There are two ways to produce ATP: the oxidative and the fermentative one.

Oncothermia heats the target like the fuel cells liberate the energy. The selection of malignant cells is made by their metabolic activity according to Otto Warburg [104], a Nobel-Laureate in Physiology. Warburg recognized the metabolic difference between the malignant and healthy cells: the malignant cells have much higher flux of glucose than their healthy counterparts do. The higher glucose metabolism needs larger ionic fluxes in the vicinity of the individual tumor-cells.



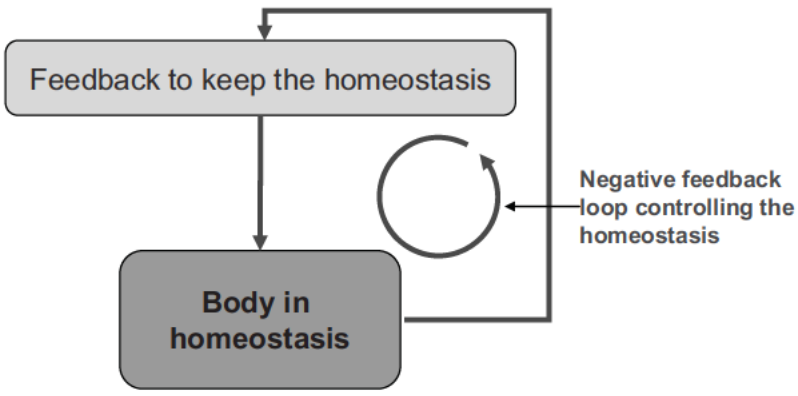
Differences of the malignant cells from their healthy counterparts

The similarities of the oncogenes activity and of the anti-apoptotic functions in cancer and in various healthy processes (like growth and reparation) are one of the most challenging facts in the present research. Due to the apoptotic processes as well as the oxidative ATP production which are suppressed in numerous growth and reparative processes degrade (at least temporarily) the function of mitochondria. This is the reason of the renaissance of the Wartburg's theory, the tumor metabolism and its mitochondrial connection is under intensive investigation, [105], [106], [107]. According to the main idea of Warburg, the primary cause of cancer is the non-oxidative glucose metabolism. Due to the fact that oxidative metabolism is the task of the mitochondria, the missing oxidative metabolism is a dysfunction of the mitochondria. According to Warburg, the mutation of the genome is a consequence of the fermentative metabolism: the hypoxia causes malignant transformation.

The electric properties of the cancerous cells definitely differ from normal. The main differences are:

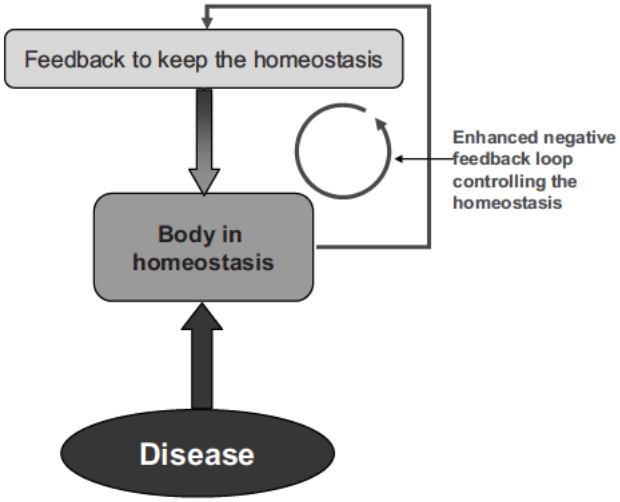
1. The efficacy of the ATP production in the cancerous cell is low. The large ATP demand for the proliferative energy-consumption allows less ATP for the active membrane stabilization by K^+ & Na^+ transport, so the membrane potentiating weakens [108].
2. The cellular membrane of cancerous cells differ electrochemically also from the normal, moreover its charge-distribution deviates [109].
3. The membrane of the cancerous cell differs in its lipid and sterol content from their healthy counterpart [110].
4. The membrane-permeability is changed by the above differences. In consequence of these, the efflux of the K+, Mg++ and Ca++ ions increase, while the efflux of Na+ decreases together with the water-transport from the cell. Accordingly, the membrane potential of the cell decreases further [111]. (The efflux of K+ regulates the pH of the cell, takes the protons out of the cytosol.) The concentration of Na+ increases in the cytosol, and parallel to this the negative ion-concentration also grows on the glycocalix shell, decreasing the membrane potential and the tumor will be negatively polarized in average, [112]. This fact was well used for direct current treatment (electro-chemical cancer therapy (ECT)) by Nordenstrom and others.
5. The conductivity (σ) and the dielectric constant (□) of the tumor tissue will be higher than normal, [113].

Oncothermia [3] applies microscopic energy liberation at the cell-membrane of the malignant cells, select them by their higher electric conductance. Oncothermia is a kind of hyperthermia with microscopic heating processes. Instead of the undistinguished cells by the classical overall heating of hyperthermia, oncothermia microscopically selects and attacks the malignant cells. It has a simple setup. The modulated radiofrequency current (RF) flows through the lesion.
Oncothermia is natural therapy. It helps the body's internal corrective actions to reestablish the healthy state. In normal healthy state the body is in homeostasis, which is controlled by numerous negative feedback loops, making the actual state definitely "constant" despite its energetically open status.



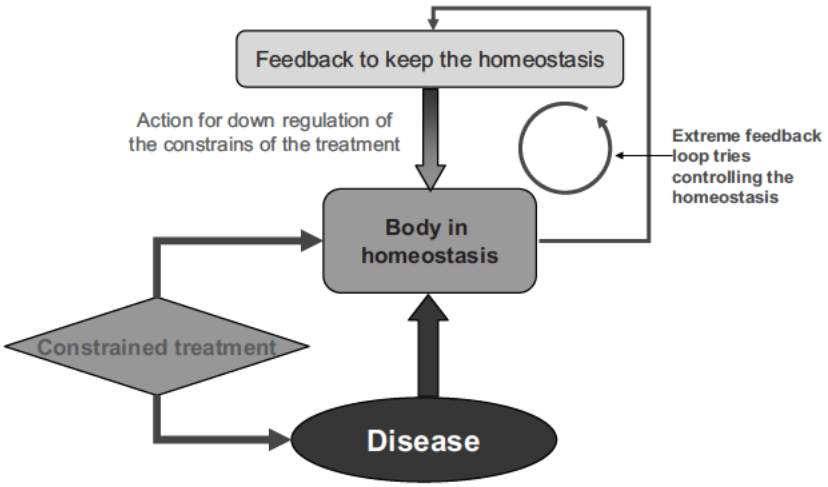
The natural healthy state is stabilized by the negative feedback loops of physiology

The disease breaks up the relative equilibrium, and the body tries to reestablish the homeostasis. For this enhanced negative feedback control is enforced.



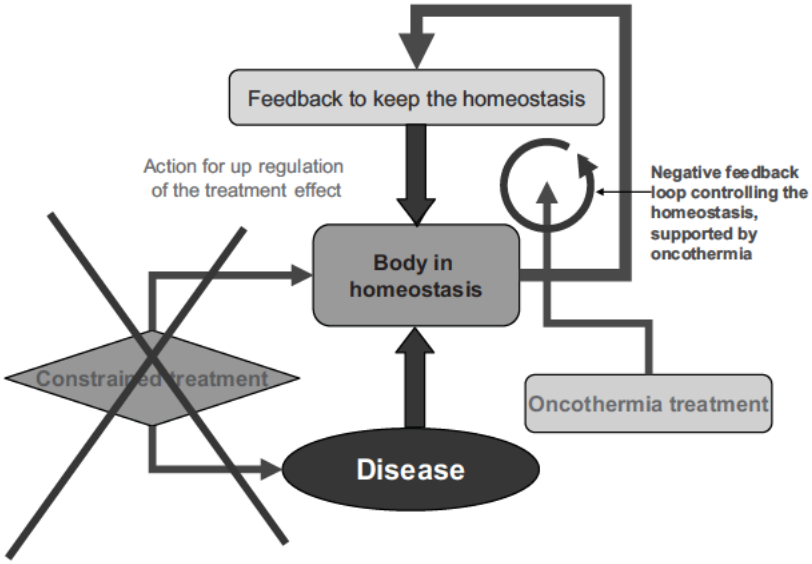
The disease breaks the homeostasis, so the physiology tries to compensate and correct the damage

Recognizing the disease, we act with our medical knowledge, and in many cases, we work against the natural homeostasis, the constrained action induces new homeostatic negative feedback. The body starts to fight against our constraints together with the disease.



The classical hyperthermia introduces a new constrained effect which induces even more physiological feedback, forcing the body for the "double front" fighting

This controversial situation occurs with classical hyperthermia, when the constrained massive temperature change is physiologically down-regulated (or at least the physiology works against it by the systemic [like blood-flow] and local [like HSP] reactions). Oncothermia disclaims the old approach, introducing a new paradigm: with the application of micro-heating it induces considerably less physiological feedback to work against the action, and with the application of the electric field it uses such effect, for which the body has no physiological answer. With this new paradigm, oncothermia helps the natural feedback mechanisms to reestablish the healthy state.



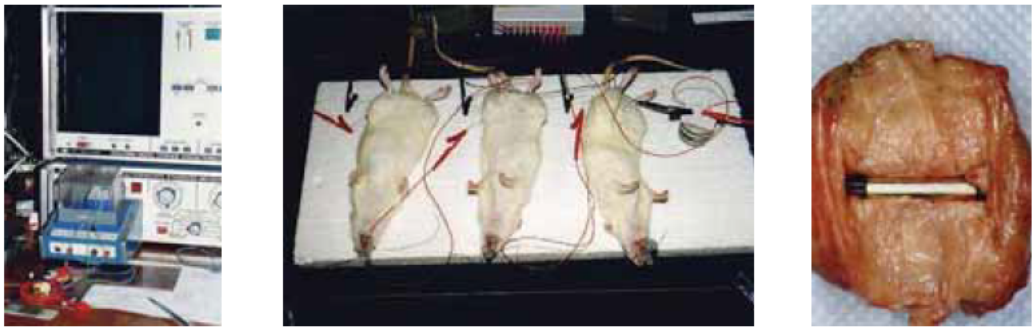
Oncothermia acts differently. It helps the natural feedback loops for natural corrections

Development of oncothermia technique

The capacitive coupling of hyperthermia heating has a long history, having its start together with the dawn of the electric treatments. The first amateur sets for experiments were done in our flat in Budapest.

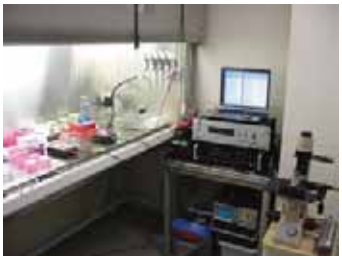
The first technical probes in our family's flat in Budapest

Oncothermia used the current density from this knowledge, and in the very first experiments made invasive electrodes to provide the best available effect on bio-materials in vitro and in vivo. The research of course was started in the laboratory.



Some experimental setups in 1989

The conditions of the experiments have changed a lot.

Experimental setups in past and now

The fragments of life in the company show activity in all the lines.

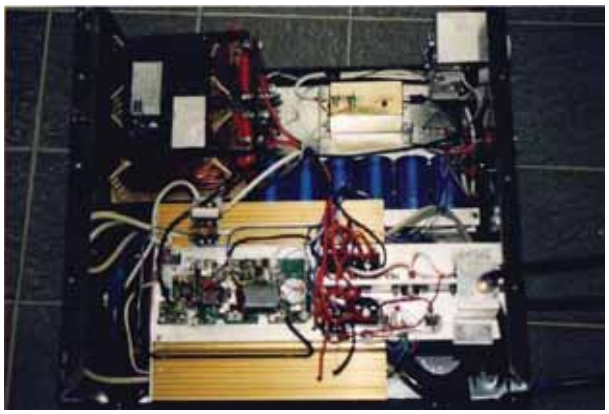





Some electronic preparation and production photos

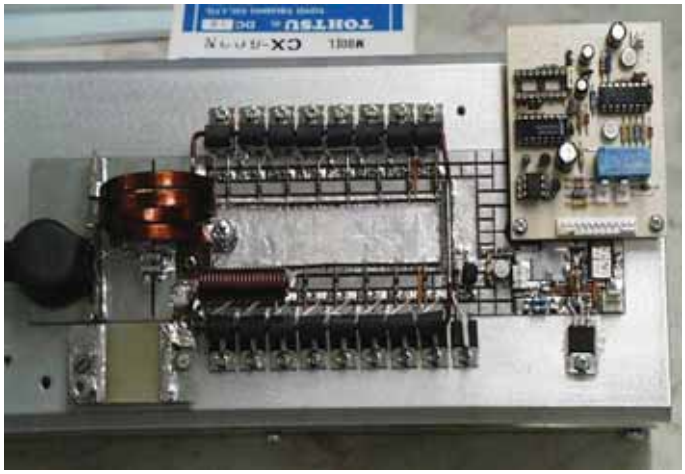
Change of electronics

Oncothermia specialty is its own internal parts, designed for special applications of oncothermia. There are much commercial availability to by RF-amplifiers, tuners and all the blocks for RF-power-supply for capacitive antenna coupling. This is usually done by the producers of classical hyperthermia. However, oncothermia is different. Due to its special modulation requests and the multiple negative feedback control inside; Oncotherm developed all the parts of the system for its own: the amplifier, the tuner and the overall controlling and adjusting unit are all own products together with the modulator the filters and all the safety controllers. At the very beginning (until 1991), the RF-source was based on high-power vacuum tubes. Soon it was realized that this solution is not safe enough. We decided on the low-voltage solid state application.
We started to use American and Japanese ready RF sources, like others did, however, the appropriate oncothermia effect could not be produced. (1991-1993)
The first own construction of amplifier was not stable enough, but its safety was well improved.



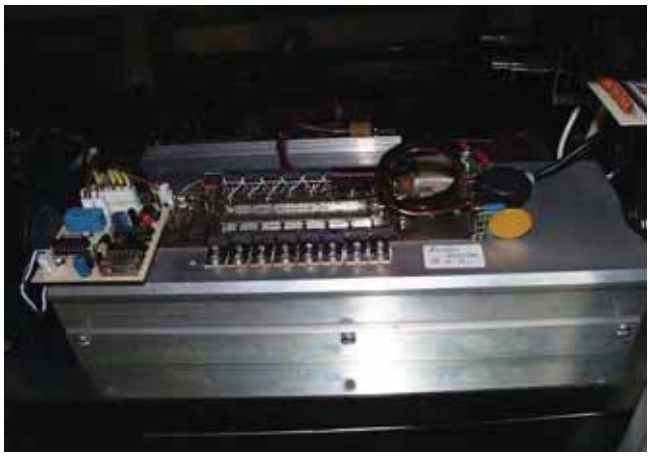
The first traditional solid-state RF amplifier. (1991)

The first, OncoTherm-made, "non-traditional" solid-state RF amplifier (two-line tandem) was constructed in 1994. It was our standard for a long time. It was stable for the 8 hours continuous treatment a day.



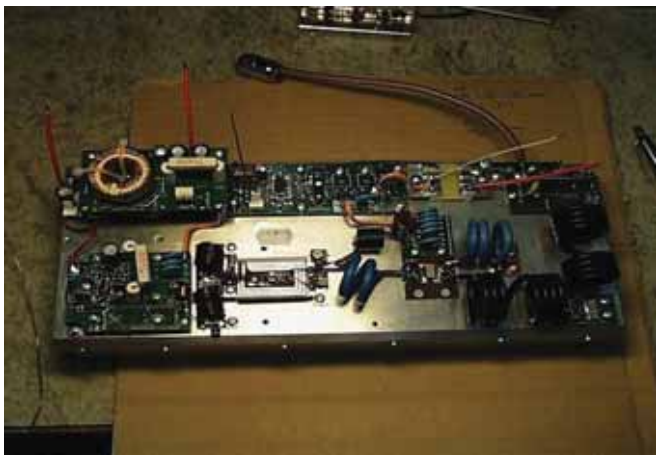
The first OncoTherm-made, "tandem" solid-state RF amplifier. (1993)

The rapid development in the solid-state electronics forced us to develop. The next was the one-line amplifier. (1998). This had less errors in calibration and longer time of daily continuous work.



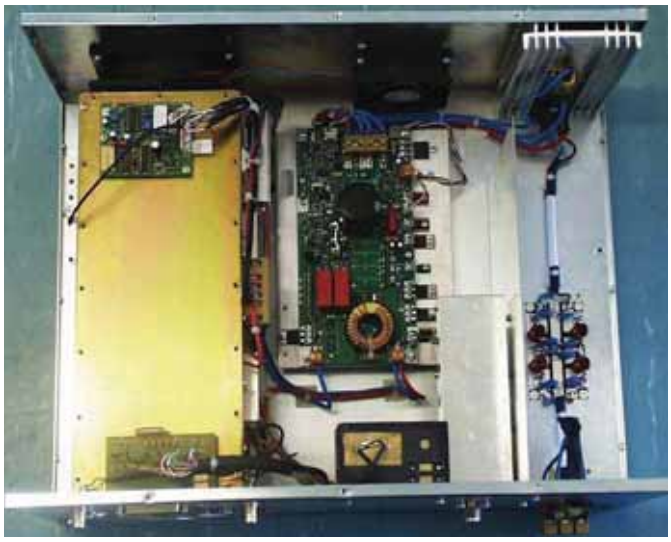
The first OncoTherm-made, linear (A-class) solid-state RF amplifier. (1998)

Oncothermia became a popular treatment. New, heavy-duty RF-source became the request. (2003) This solution could tolerate even a short circuit at the end, and could work without stop day and night.



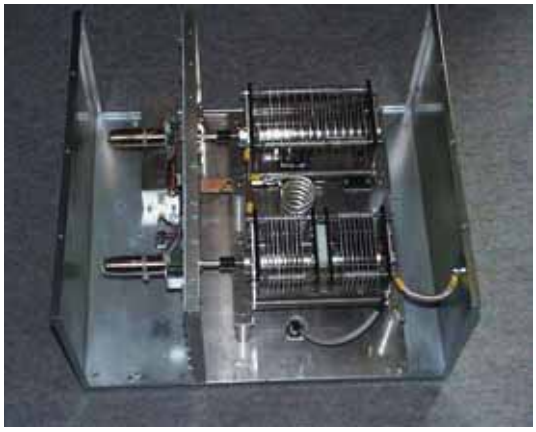
The first OncoTherm-made, E-class solid-state RF amplifier. (2003)

At present a high-efficacy extra stable and safe, highly unified amplifier has become the OncoTherm standard. (2005). This satisfies the most rigorous EMC standard: it could be applied in any of the living environments. This opened the way for EHY2000+.



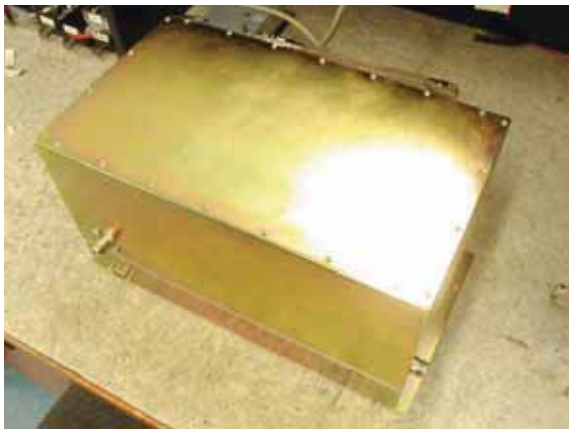
The high-level OncoTherm-made, new-principle E-class resonant solid-state RF amplifier. (2005) (The main unit of the amplifier is in the shielded box at left-hand side.)

In the meantime, the tuner was also developed. It has a sophisticated software to approach the optimum matching, to quickly follow any change during the treatment. It is one of the crucial factors of the optimal and selective energy delivery.



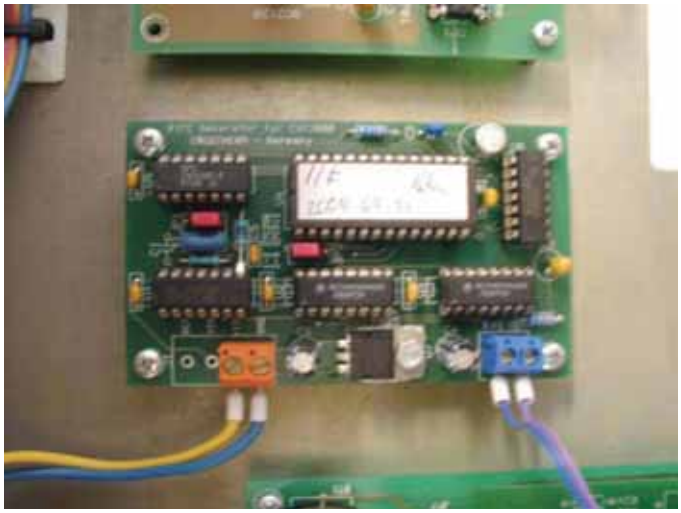
The high-preciosity 8kV automat matching unit

The new matching has a quick tuning reaction to follow the movements of the patient. For laboratory devices an ultra-low reaction-time tuner is developed, to be able to follow the heart-rate of the animal. This is a revolutionary solution in the matching.



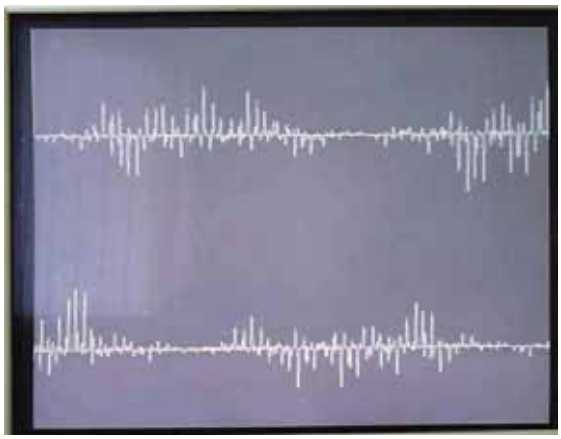
The new tuner for quick reaction

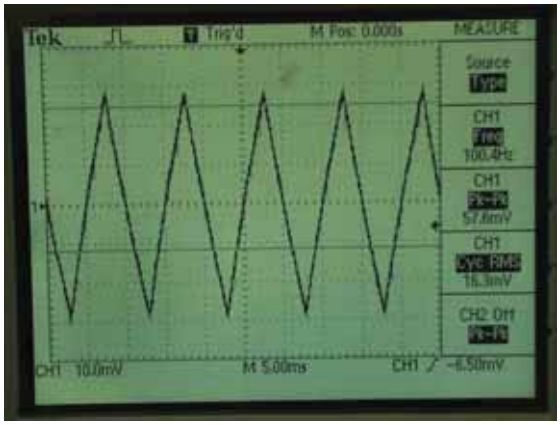
The modulation solution (patented) is very specially designed for the best available efficacy to individualize, personalize the treatment



The modulation unit of the EHY systems

The modulation signal is a time fractal, and has a special feedback mechanism for the requested performance.



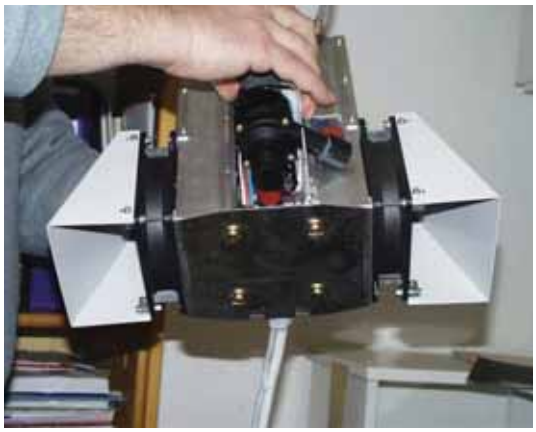
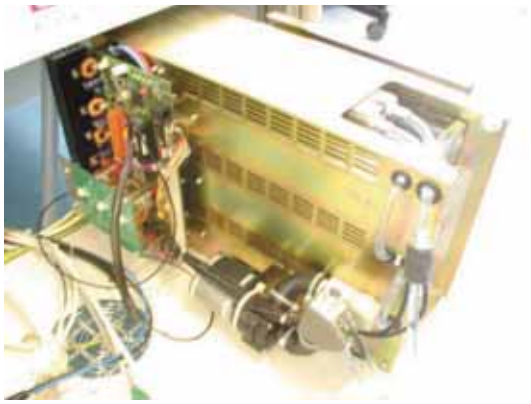


Parts of the modulation signal in the internal working feedback

The cooling also has some well defined tricks. It is special, physiologically fitted solution (patented). It has been improving gradually from generation to generation, which is critical for safety and efficacy optimizing.

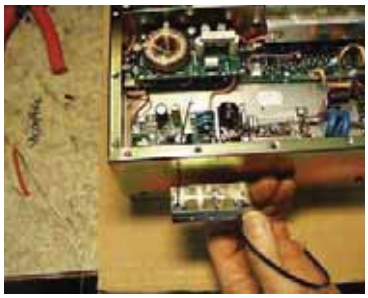
The cooling unit in EHY2000 systems

The improvement of this unit directly appeared in the final efficacy rate.

Various cooling units in the EHY2000+ systems

The evolution of the device solved the emission and interference problems, and the outside shielding was not necessary any more. The ultra-small emission, (the attenuation is under 120 dB), small interference and complete immunity is the result. Our newest design is certified to be used in living rooms.

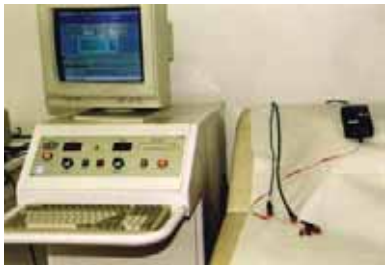


HighTech filter solutions in EHY devices

Development of the devices

The direct current experiments led us to the first device: the ECT (Electro-cancer-therapy). Of course these devices have the fractal modulation too, as the basic selection tool.

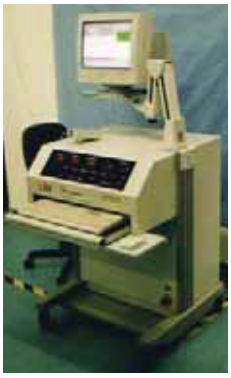




The first two experimental systems of ECT, named DUCAT

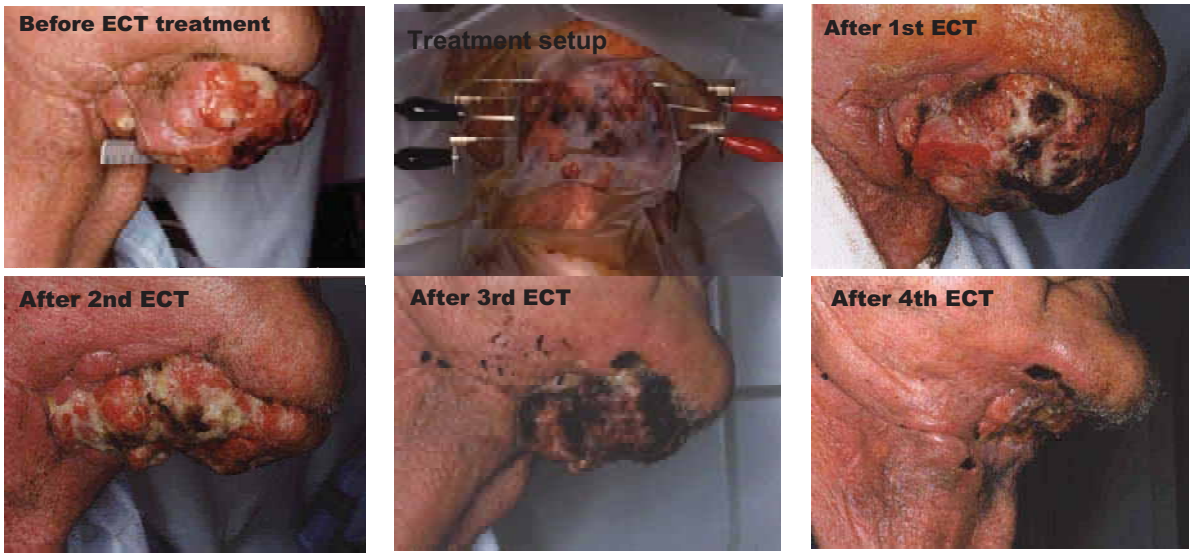
The more developed systems has TUV [Munich] approval (GS-certificate).





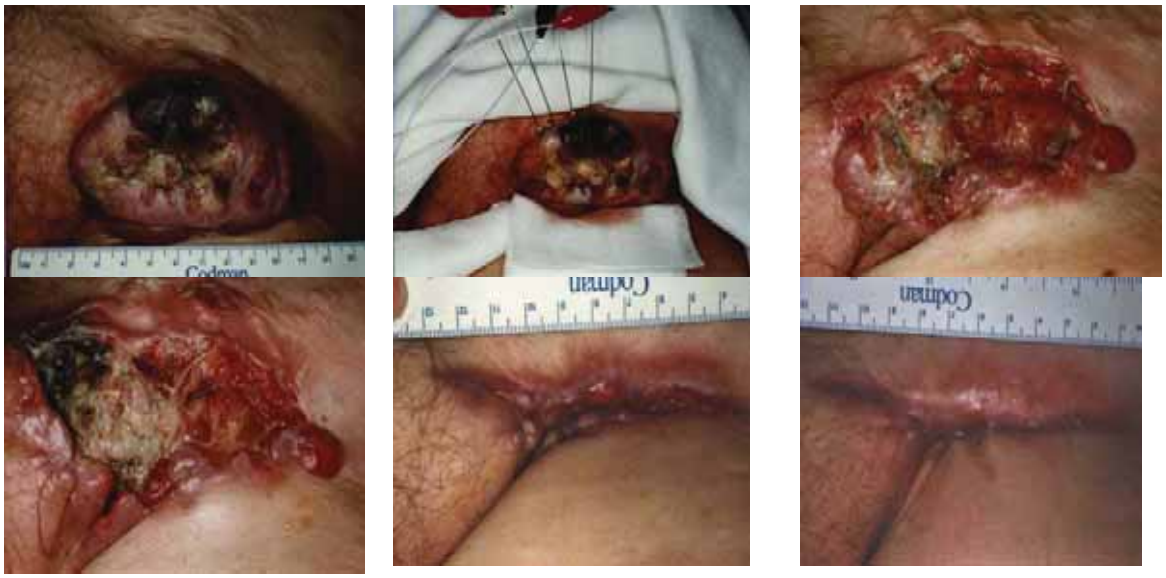
Some variants of ECT device, firstly approved by TUV GS-certificate

ECT had very good results. Inoperable advanced cases were successfully treated, weapplied less than 5W (no temperature).



Inoperable submental local recidive of planocellular carcinoma (tumor under the chin) (male 61y) [Dr. L. Patonay, 1994, max. 5W]

Extended applications were tried. Some of the devices are working even nowadays 15 years after its installation.



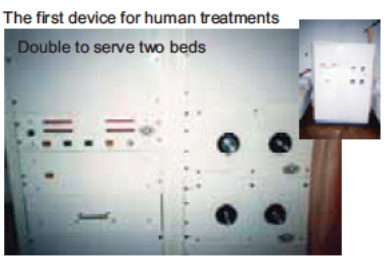
Inoperable carcinoma papillare (inguinal region, female) [Dr. L. Patonay, 1994, max. 5W]

The results were so promising, that the first international symposium was organized.


THE FIRST INTERNATIONAL SYMPOSIUM
ON ELECTROCHEMOTHERAPY OF CANCER

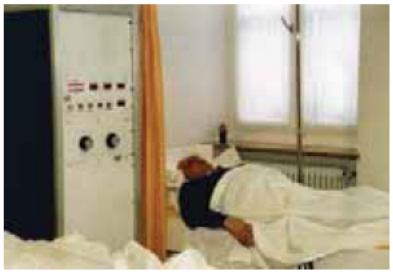
The first international symposium of ECT was held in Beijing, China, in 1992

However, ECT was a huge medical challenge. It was invasive, so its application was limited to the near-surface region. The invasive application had dangerous risks by its application in sensitive organs like the liver. The risk of bleeding, inflammation and infection was also a great challenge. We decided to develop a non-invasive solution.
The well- known (and long time applied) capacitive coupling was chosen to pump enough current into the body. The carrier frequency was the well- known (and applied by many other producers) 13.56 MHz, which is a free frequency for medical use. The name of the non-invasive devices became EHY (electro-hyperthermia). [This name was used later by other manufacturers, using definitely different technique, without the patent-protected fractal modulation.



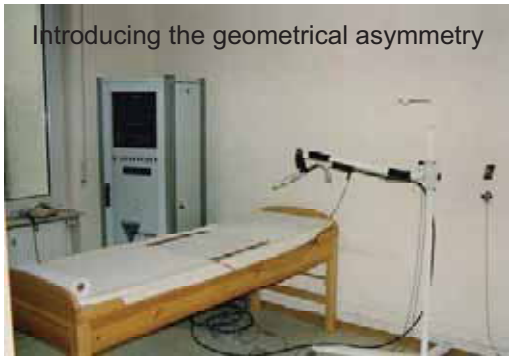
The first EHY devices (name was also DUCAT) from early 1992.

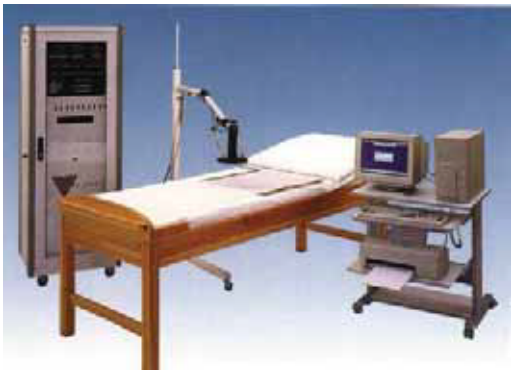
This is the reason why we emphasize the original oncothermia way in our products. Due to the problematic tuning in that time, we applied special, wooden beds for treatments.



Installations in Clinic St.Georg, 1992-1996

The symmetric electrode system had some disadvantages (mainly the risk of adipose burn), so we developed the asymmetric solution.



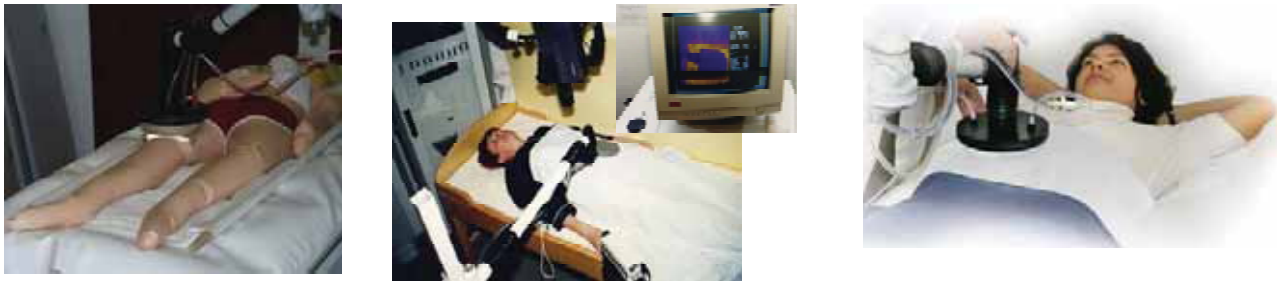


Asymmetric electrode solution solved the problem of the adipose burn

The modern EHY2000, EHY2000+ and EHY2010 systems are the most popular devices for oncothermia.

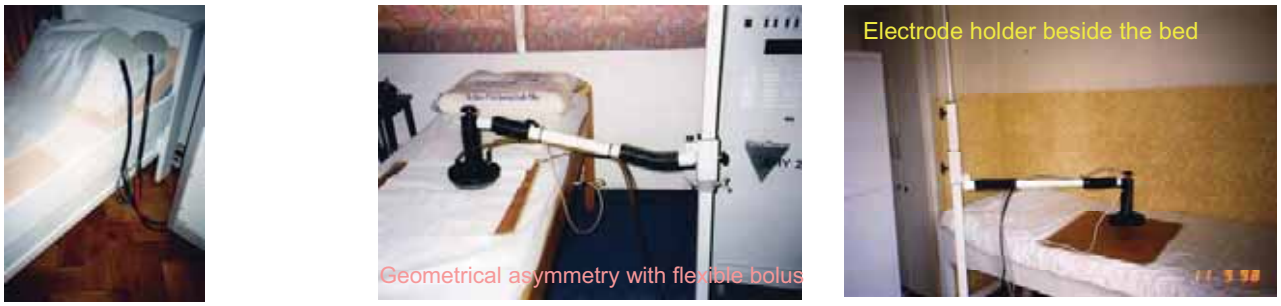
The EHY2000 series (EHY2000, EHY2000+, EHY2010)

The key element of oncothermia technique is the electrode system. There is a slogan in the company: ”Oncothermia starts at the electrodes.” Indeed, the electronic power-supply is a simple technical issue compared to the electrode system. The materials, the construction and the impedance fitting are all important factors, having long, very systemic experimental and theoretical work.



Some experimental setups for electrode optimizing

The fields of various electrodes was also measured carefully by electromagnetic compatibility .

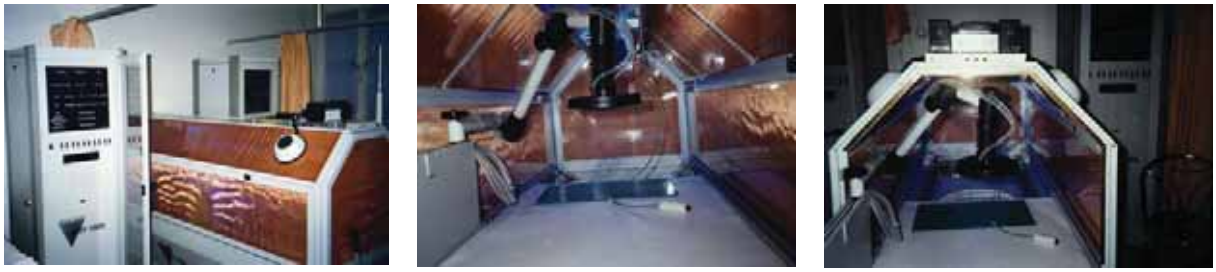


Special solutions for electrode for EMC measurement

It was a special new challenge due to the electromagnetic compatibility problems: the shielding. Oncotherm has developed numerous solutions for shielding the room.

Room shielding to solve the requested electromagnetic compatibility

The room-shielding was very complicated and expensive. The local solutions were also not satisfactory; the patient had claustrophobia.

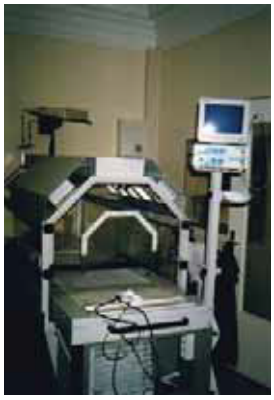


The local shielding systems of EHY2000 devices in 1995

In the end, we solved this problem electronically. The developed different bolus electrodes were satisfactory for the best electromagnetic compatibility tests in TUV-laboratories (Mikes ,Germany). Oncotherm received the best evaluation of EMC, allowing its use even in living areas.

Various bolus electrodes developed for EHY2000 series

The new challenge was the whole body treatment. It was developed, because most of the patients had distant metastases when oncothermia was started. The technical solution was very new, special, patented, layered structures did the filtering for infrared-A radiation. The device provided very good results in a specialized study (Dolphin study) in Ludwigs Maximillian University, Munich, Germany.


Development of the WBH systems, the first prototype, the first WBH2000 and the MSH2000

Despite of its success, the WBH system was too complicated to use, and due to its extreme heating (up to 42 ^{o}C) it was risky as well. Oncotherm abandoned this field of activity.



The fully developed WBH2000 extreme whole-body system and MSH2000 moderate whole body system from Oncotherm

There were many new challenges in the market. Invasive interstitial device was one of the requests, so Oncotherm developed its device (ICT2000)

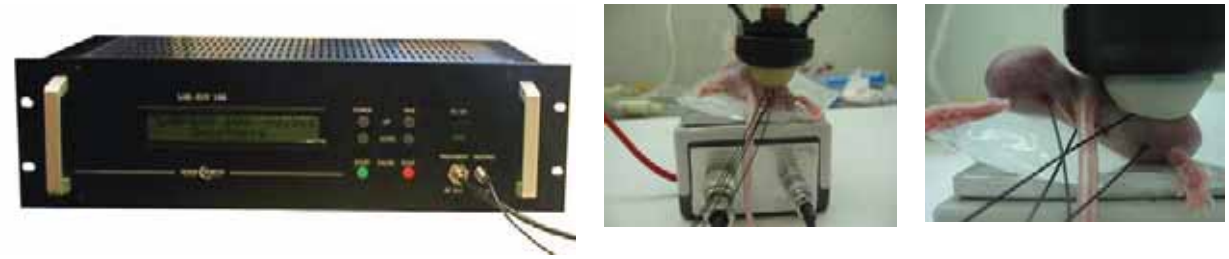

The interstitial tumor therapy device: ICT2000

The experimental work became more and more important in the life of the company. We developed the EHY105 for in vitro laboratory experiments.



EHY105 experimental laboratory unit for in vitro experiments

The demand for the in vivo preclinical studies was also pressing us to develop new laboratory device for in vivo studies. The EHY110 was launched in 2005.



EHY110 experimental laboratory unit for in vivo experiments

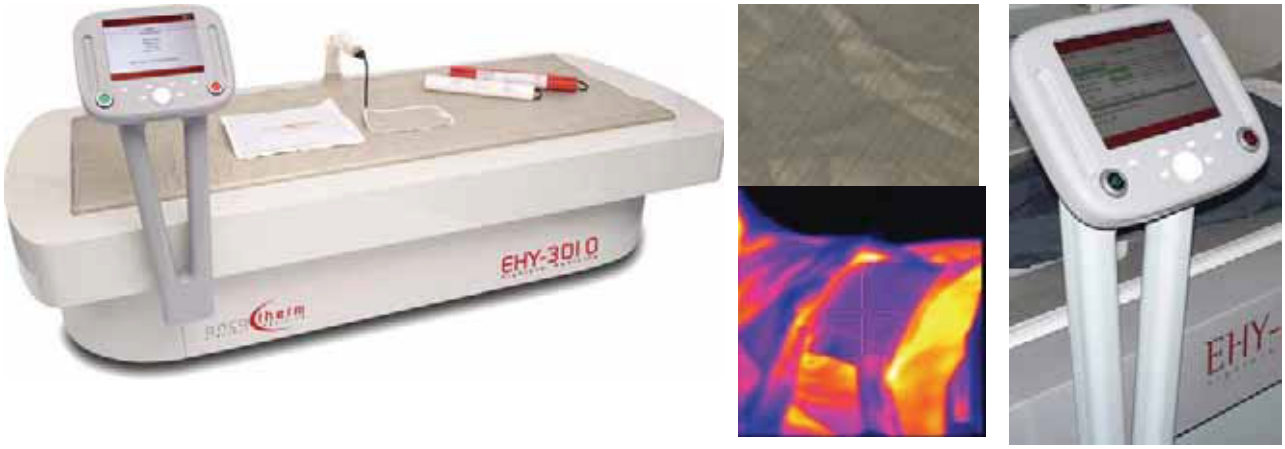
We had the PCT2000 device for transurethral prostate treatment in 1997.

The first devices for transurethral prostate treatment (for both the benign and malignant tumors), 1997

An old challenge was renewed: the intraluminar oncothermia was requested by the market. We developed the new series of intraluminar oncothermia.

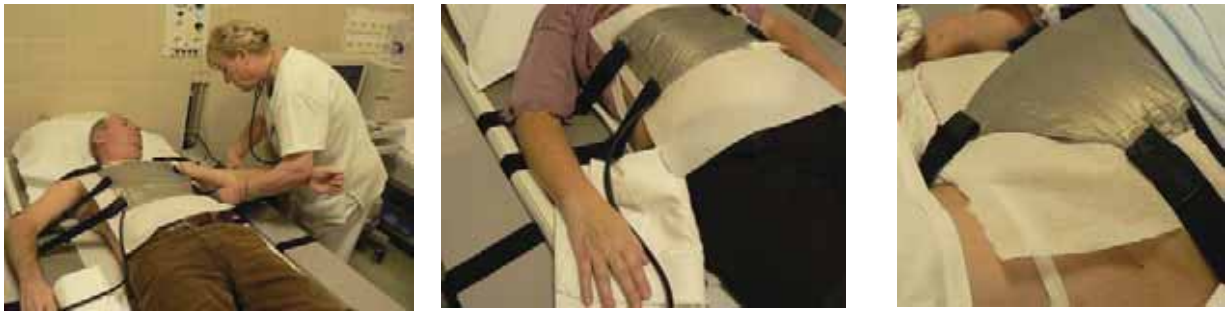
EHY1000 and EHY1020 transurethral oncothermia device, and its catheter

We developed a revolutionary new device, which is unique on the market: the EHY3000 series. It is a multi-local treatment, capable of treating distant multi-local metastases parallel with the primary tumor treatment. The treatment targets only the malignancies all over the treated volume by the well-known selectivity of oncothermia. It is not capacitive coupled, it has direct impedance coupling with special (patented) electrodes. (Again, the key factor of Oncothermia is the electrode in all applications.)



The EHY3000 series of oncothermia. It is revolutionary new. The electrode is air-cooled, direct impedance fitting (no capacitive bolus)

The electrodes of EHY3000 series are freely shaped for the patient's specialties.



The size and shape of the electrode could be formed according to the patient's body-form

The electrodes are easy to fix and it is possible to treat parallel distant metastases, even in the whole body.

Using EHY3000 system is easy to fit for any metastatic places also

There are absolute new challenges on the market on the side of chemotherapies: the targeted chemotherapy. Oncotherm developed a new device for chemo-targeting (Booster), which makes deep heating of the target inside the body. (It has no focus, works like classical capacitive hyperthermia device made by any producer. It has presently 80W power, but it could be increased easily to much higher power values in the desktop model.)

The Booster for chemo-targeting form Oncotherm

Oncotherm tries to satisfy other, not oncological requests. One example of this is the AndroTherm device, developed for andrological diseases like Peyronie disease.

The AndroTherm device to treat Peyronie disease

The new development of Oncotherm the VetEHY system for small animals (pets like dogs, cats, hamsters, etc.). This device is used not only for veterinarian applications, but it is an important tool for preclinical investigations too.

The VetEHY device for small animals (dogs, cats), and for preclinical investigations

Various tumors of dogs are treated with this device.


Theratments by the VetEHY device

Oncothermia results

Oncothermia is a complementary therapy. It is applied together with all the "gold standard" oncotherapies. These complementary standards are the oncosurgery (pre- [adjuvant, neoadjuvant] and post-operative therapies), radiotherapy, to boost the blood-flow (oxygenation); oncothermia is applied pre-radiative, beeing a synergic supporter, it is used as post-radiative therapy). Oncothermia is a has complementary application with chemotherapy, boosting the drug delivery. The new therapies (like immuno-therapies, dendritic-cell treatments, stem-cell treatments, gene-therapies, virus-therapies, etc.) are all applicable together with oncothermia. Its application as monotherapy is only possible when the gold standards failed (resistance, kidney of liver failure, blood-count problem, etc.). In this case, it is a palliative method. In most of the cases, oncothermia is applied in high line treatments due to the possible satisfaction of the gold-standard therapies in first-, second- and even third-line. The fourth line application of oncothermia is general, no contraindication could be listed due to the stage of the patients. Oncothermia could be applied in all tumor-kinds, including the sensitive brain and the central nervous system, as well as the well-cooled lung or liver. The various cases are shown on the Oncotherm web-sites, or could be posted in detailed electronic form upon request.

There were numerous studies published. 42 studies covers data of 2054 patients from4 countries and 14 different clinics. All data were publsihed at least at various conferences including such international one as ASCO.

No	Study	n	1st year survival (%)	Median overall survival (m)	Responsn ding patients/ ratio (%)	Median overall survival of respondin g patients (m)	Median overall survival of non-respondin g patients (m)	OER	Place
1	Bone-metastases 1	11			90.9				Reinkenheide, Bremerhaven
2	Bone-metastases 2	6		40.1					HttMed Clinic
3	Breast cancers	103	97.1	52.1	45	274.8	10.9	25.2	HttMed Clinic
4	Colorectal cancer (rectosigmoid junction)	12			34.1				Peterfy Hospital
5	Colorectal cancer (rectum)	92			57.1				Peterfy Hospital
6	Colorectal cancer (rectum)	114			44.2	109.8	23.2	4.7	Peterfy Hospital
7	Esophagus study 1	12	41.7	28.49	35	29.4	8.5	3.5	HttMed Clinic
8	Esophagus study 2	7		6.8					Nurnberg Nord, Clinic
9	Glioma efficacy study 1.	27	86.2	23.6	43	66.2	18.2	3.6	HttMed Clinic
10	Glioma efficacy study 2.	140	71.7						Witten-Herdecke University
11	Glioma efficacy study 3.	45		15					Nurnberg Nord, Clinic
12	Glioma efficacy study 4.	19	68.0	21.8	59	32.6	12.4	2.6	St.Georg Clinic
13	Glioma efficacy study 5.	36	60.0						BioMed Clinic
14	Glioma efficacy study 6.	179							BioMed Clinic
15	Glioma efficacy study 7.	12		10	25				St.Giuseppe Hospital
16	Glioma toxicity study	24							Regensburg University,
17	Head and neck	64	92.2	26.1					HttMed Clinic
18	Kidney cancer	39	84.6	35.9	48	78.4	33.7	2.3	HttMed Clinic
19	Liver metastases from vaious origine 1	25		20.5					HttMed Clinic
20	Liver metastases from vaious origine 2	28							Reinkenheide, Bremerhaven
21	Liver metastasis form colorectal origine 1	80	86.0	24.1					BioMed Clinic
22	Liver metastasis form colorectal origine 2	15			80				Siloah Clinic
23	Liver metastasis form colorectal origine 3	30		22					Spedali Civili Brescia
24	Liver metastasis form rectal origine	29							Semmelweis University
25	Lung cancers (Adeno + small-cell)	67			47.7				Yonsei University
26	Metastatic brain study	15	90.0	46.2	73	48.2	16.1	3.0	HttMed Clinic
27	Non-small cell lung cancer meta-analysis.	311	67.0		21	53.4	18.1	3.0	St.Borbala Hospital
28	Osteo-sarcoma	62							St.Georg Clinic
29	Pancreas tumors 1/a	73	52.1	9.93	58	25.5	8.4	3.0	Peterfy Hopital
30	Pancreas tumors 1/b	26	46.2	11.6					HttMed Clinic
31	Pancreas tumors 2	30	31.0		41	34.4	5.6	6.1	St.Georg Clinic
32	Pancreas tumors 3.	42	52.4	12.3					VeraMed Clinic (Meshede)
33	Pancreas tumors 4.	13	40.0	11.9					Nurnberg Nord, Clinic
34	Pelvic gynecological cancers (cervix)	38	86.8	27.6	25	63.5	20.9	3.0	Peterfy Hospital
35	Pelvic gynecological cancers (ovary)	27	100.0	37.8	67	132.7	19.4	6.8	Peterfy Hospital
36	Pelvic gynecological cancers (uterus)	9	100.0	61.5	62	68.5	32.0	2.1	Peterfy Hospital
37	Prostate cancer	18	88.9	38.8	72	53.4	7.6	7.0	HttMed Clinic
38	Rectum carcinoma	7			71				Nurnberg Nord, Clinic
39	Rectum carcinoma	65							Semmelweis University
40	Soft tissue sarcoma	16	100.0	35.9	31	115.3	31.3	3.7	Peterfy Hospital
41	Somach study	68	58.9	14.4					HttMed Clinic
42	Urinary bladder cancer	18	85.0	36.5	73	42.0	22.6	1.9	Peterfy Hospital

In addition, there are a whole-body hyperthermia study (Dolphin, Ludwigs-Maximillian University, Munich, Germany) and the prostate study (St.George Clinic, Bad Aibling, Germany). Large number of published scientific and medical (in silico, in vitro, in vivo) studies support oncothermia, including a book published by Springer Scientific.

Presently (2011) one ongoing controlled randomized clinical study is in progress. One is for advanced, relapsed or refractory breast cancer (Mammatherm, Ludwigs-Maximillian University, Munich, Germany). Two controlled randomized studies are in preparation phase:
1. OvaTherm Korean National Cancer Institute, Seoul. It deals with advanced, refractory, relapsed ovary cancer.
2. PancroTherm McMaster University, Canada It deals with advanced, R1 or R2 surgery status, relapsed or refractory pancreas cancer.

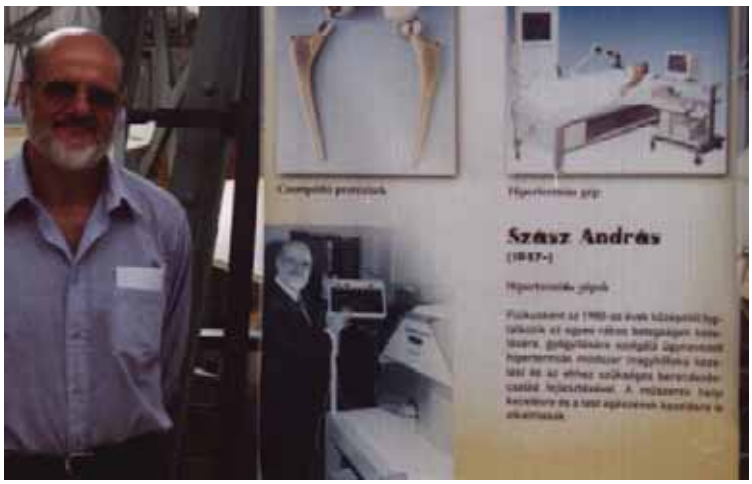
There are some ongoing preclinical studies.

In vivo:
1. Veterinarian effects (dogs, cats) Tottori University, Japan
2. Ecchinococcus treatments Dusseldorf University, Germany
3. Bystander effects of oncothermia Chiba University, Japan
4. Immuno-effects of oncothermia Semmelweis University, Hungary
5. Oncothermia improvement Joliot-Curie Institute, Hungary

In vitro:
1. Selective cell-destruction mechanisms Semmelweis University, Hungary
2. Viral effects St. Istvan University, Hungary (planning phase)

In silico:
1. Correlation, selection effects Pazmany University, Hungary
2. Electric field distribution effects Pazmany University, Hungary

Dreams are realized



I am in the exhibit of "Dream dreamers Famous Hungarians"

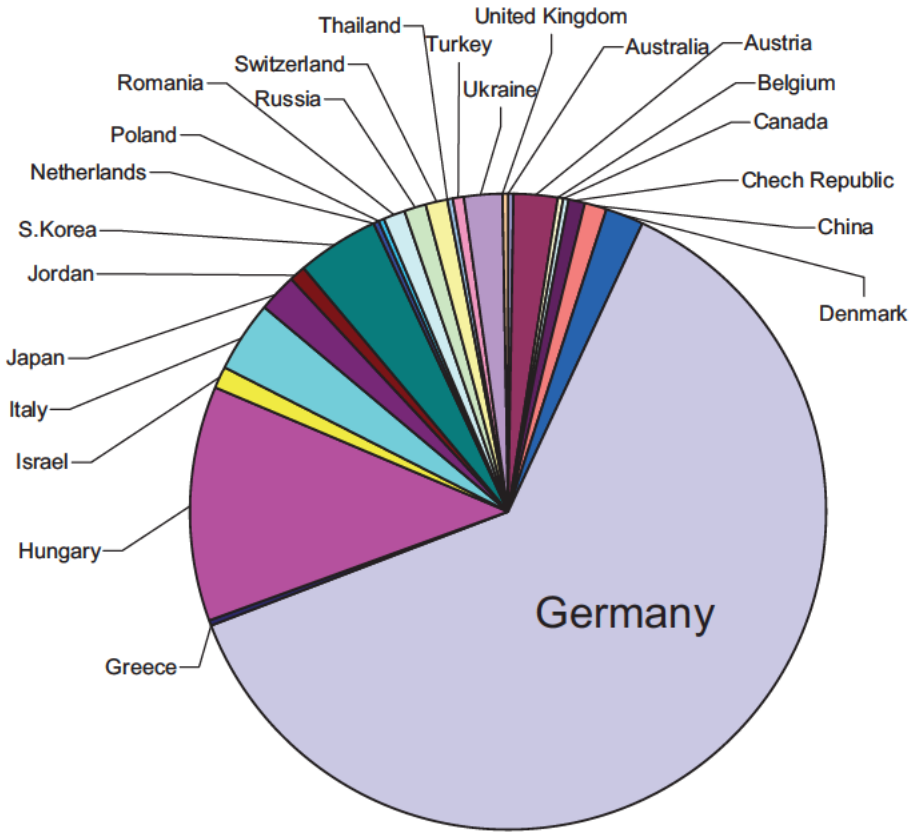
My son, Oliver, receives the Innovation price on behalf of the Oncotherm.

The CEO of Oncotherm, Dr. Oliver Szasz take up the Hungarian Innovation Price

Our company had good evaluation by independent observers.

Oncotherm was among the 100 "small tigers" in Hungarian business evaluation

We have developed 18 types of devices in 7 categories during the history of oncothermia. We have produced ~300 devices and delivered it to 24 countries. Some of these are out of our control. Recently we actively control 220 devices in 19 countries.



The countries, where oncothermia devices were installed until 2011

We have a large distributor-network involving all continents of the world.

Oncotherm in Asia

Concluding remarks

Hyperthermia is an ancient treatment. It was the very first one in oncology, but it could not find its established place among the "gold standards" of the oncotherapies. The controversial results were originated from the paradigm to constrain the temperature growth in the process. The constrained forces made physiological contra-reactions to keep the homeostasis, which unfortunately contains the malignant tissue as well. The actions have to be selective, and have to be gentle enough to work together with the natural processes, and not against them.

Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat-flow on the membrane supported by the electric field effects). It is natural, it is not against the homeostasis, physiology does not work against the action. The main task is to direct the physiology in the standard way, and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium have to be stopped.
Oncothermia follows the update demands of the modern oncology:

6.It is personalized therapy,
7.It is non toxic,
8.Elongates the survival time of the patients,
9.Completing the curative actions with increased quality of life
10. It has good cost/benefit ratio

The introduced new paradigm solved the classical challenges:

■ **Challenge (1)**: "The biology is with us while the physics is against us" (Overgard J., **[23]**
✓ ***Oncothermia solution:*** "The biophysics is with us"
■ **Challenge (2)**: "The biology and the physics are with us while the physiology is against us" (Osinsky S., **[24]**)
✓ ***Oncothermia solution:*** "The fractal physiology is with us"
■ **Challenge (3)**: "Reference point is needed!" (Fatehi D. van der Zee J., et. al. **[39])**
✓ ***Oncothermia solution:*** "Back to the gold standards, use the energy instead of temperature"

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