Oncothermia Journal 9:55-69 (2013)

Past, Present and Future of Oncothermia

Szasz O.[1]
(1) Depertment of Biotechnics, Faculty of Engineering, St. István University, Budapest, Hungary
(biotech@gek.szie.hu)

Past, Present and Future of Oncothermia

Abstract

Oncothermia is a new type of cancer treatment that was introduced 25 years ago, in 1988 as a spin-off from the Budapest Science University, "Eotvos Lorand". The long journey of this idea and company together with the perspectives is described briefly in this paper.

Introduction

My grandmother died in cancer when she was young. She could not see her grandchildren; she died when my father was a student. She suffered a lot, but there was no help. After graduation in physics, my Father started working at Science University, there was no chance to work in the field of cancer. His topic was apparently far away from any biology, he focused his research on surface and interface physics. He successfully published and patented many theoretical and practical solutions in his field, working in labs not only in Budapest, but in the Zhdanov University of St. Petersburg and later in Strathclyde University, Glasgow as well. His research was concentrating more and more on the instable and metastable states at the surfaces, and direct way was to the biological membranes. He published a lot about the metastable and instable states at surfaces and also the connected biological phenomenon was in his consideration.

A special idea of the membrane instability (anyway connected with the high-temperature superconductivity) was considerably studied by him in Glasgow, and he came home to establish a company devoted to this idea. After a long battle making a spin-off company from the university in the socialist Hungary, which had not legal entity for private corporations, he established Oncotherm (at that time the name was Surface Research Ltd.). This was established on the law of pre-war Hungary from 1930. The funding of the company was helped by his mentor, academician Prof. Emeritus Dr. Elemer Nagy.

A year later a lucky meeting happened with Dr. Friedrich Douwes, internist-oncologist, owner of St. George Clinic in Bad Aibling, Germany. He was expert of hyperthermia and was looking for a device construction to realize it. My Father took it, and started the construction of a hyperthermia device built in the knowledge of the membrane selectivity for oncology use.

My Father was happy to work for the memory of his Mother, and abandoned all his previous physical researches, changed his University location, and habilitated in biophysics at St. Istvan University, where soon he funded the Biotechnics Department and became its first head. The complete family (my Mother who is also physicist, PhD, my sister and me) understood the importance of this topic, and all of us started to help. My Mother left her position at the Technical University, helping my Father in the Company. I started to learn programming intensively and wrote the very first operating programs for the first devices when I was 15. Later on I had my PhD on the quality and operating control of the high preciosity medical devices, and my sister had join later to this activity with her PhD topic, chosen it in bioelectromagnetics. Our activity was gifted, when my Father's sister (my aunt) developed the same cancer as my Grandmother. But the method was ready, and she was successfully treated with this in Germany, and cured. (It was 14 years ago, and she has no evidence of the disease, symptom-free from that time.)

Oncothermia is a new type of cancer-treatment targeting the malignant cells on nano-range, at its membrane and exciting basic cellular signaling pathways,

[1]. The front-line achievements explaining the cellular differences between malignant and healthy cells were well recognized in the last century but unfortunately these were not used for selection in practical applications. Our objective is to show how oncothermia had been developed and used as effective weaponry against the fatal cancerous diseases.

Method

The main problematic points of the extended applications are connected to the control of the process, the adequate dose and protocol of the method and the reproducibility of the results. "Reference point is needed" [2] was formulated by the well-known research group of hyperthermia. The development of this kind of treatment has been hectic and controversial [3]; consequently the general professional skepticism blocked its application for a long time. Numerous doubts arise with official cumulative equivalent minutes (CEM43□CTx) hyperthermia dose. It is shown "…prospective control of thermal dose, as described by CEM43□CT90, failed to achieve the projected pCR rate in high-grade soft tissue sarcomas treated pre-operative thermo-radiotherapy…." [4]. "This indicates that CEM43°CT90 thermal dose needs further exploration, before it is generally applicable across treatment centers." [5]. Many prospective clinical trials of conventional hyperthermia are questioned [6]. A recognized specialist of the hyperthermia formulated a long time ago [7]: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment." A new question arises: Have we learned enough?

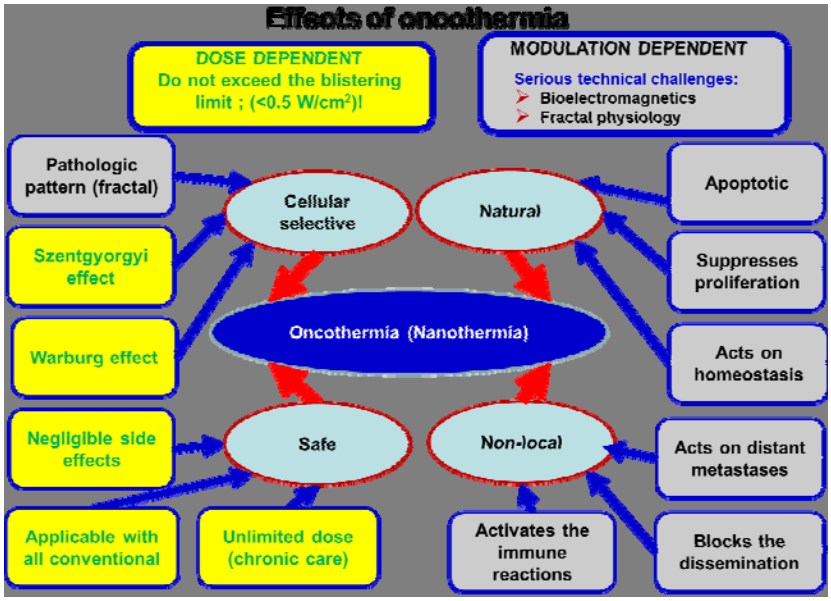
Clues for the success of the proper hyperthermia treatment are: (1) accurate selection of malignant cells, (2) avoiding the gained blood-flow (which cools, delivers nutrients and risks dissemination); (3) using effective cell-killing, (preferred apoptosis); (4) acting on immune system for support. Oncothermia offers solution for all of these requests, [**1**]. The selection of the cells is based on four strong headstones: (1) High glucose metabolism of malignant cells discovered by Otto Warburg [8]; (2) the dielectric differences of the malignant (alpha state) and normal (beta-state) cells, discovered by Warburg's student A. Szentgyorgyi [9]; (3) Beta- and delta-dispersion selection, discovered by H. Schwan [10]; (4) fractal pattern structural differences of malignant tissues, [11].

The selection is solved by nanoscopic energy liberation on the cell-membrane [12], which heats microscopically [13] non-homogeneously, keeping the system far from thermal equilibrium [14]. This effect is dominant on the cellular membrane of the malignant cells, acting by special processes [15], which are produced by time-fractal modulated radiofrequency current [16], [17]. The applied current has no noise thermal limit at the membrane [18] for heating; and so it amalgamates strong synergy between the electric field and the temperature effects [19]. It centers of its dose concept on the chemical changes [20], which promotes this emerging method [21]. Massive apoptotic signal-transduction starts from the membrane by the electric excitation [22], which is well proven in mRNA level too [23]. The important results are the possible immune effects of oncothermia [24], which could lead to a systemic action [25].

Applications of oncothermia are well proven in multiple research levels [26], [27]. The veterinarian preclinical research is an important step of course [28]. There are large number of clinical studies that show the feasibility of oncothermia [1], [29] as a complementary treatment to all other conventional oncotherapies. The method could be applied in far advanced cases too [30].
Oncothermia is a personalized treatment by tuned energy delivery to the targeted tumor; the energy is well focused on cellular level [31]. This process makes the dose of energy optimal for cell destruction [32]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized [33], [34] and is successfully applied for sensitive tumors such as advanced malignancies in the brain [35].

Oncothermia method is applied in advanced cases, when conventional therapies alone have no perspectives, when the tumor is far advanced, relapsed, or the patient developed special contraindications like liver or kidney failure, severe leukopenia or other blood-problems, multiple drug resistance, etc. It is successfully applied as monotherapy in many localizations when conventional methods fail [36].

The effects are shown summarized on the graph below.



Historical overview

IDEA: special conductive/structural properties of complex surfaces first occurred in 1986. This new hyperthermia had long way to be distributed widely. The steps are shown in the table below.

Time	**1988-1990**	**1990-1994**	**1994-1998**	**1998-2003**	**2003-2006**
Event	University spin-off	Safety approvals (TÜV-GS)	New EHY development	Market approval [CE (TÜV)]	Complete new CE/MDD for EHY
	Company start (1988)	Non-invasive electric field	Special devices (PCT, WBH)	ISO9001, ISO 13485	EU grant (financial support)
	"Garage" company	Complete company structure	Preparation of CE-mark	Organizing of the marketing	Opening HOT OncoTherm
Science	Bio-electric currents	Bio-electromagnetism	Modulated electric field	Colour-noise bio-activity	Prospective clinical studies
	Injury-current	RF field propagation	Heating/cooling optimizing	Extracellular thermodynamics	Regular university seminars
	Positive feedback loops	RF antenna couplings	Bio-physical calculations	Retrospective clinical studies	Studies of electric-thermal limits

Construction	Invasive electric field	Symmetrical electrodes	Extended safety solutions	Entire asymmetry	Medical state-of-art upgrade
	DC and time-sharing AC	Manual antenna-matching	New electrode system	Special safety features	Complete technical reconstruction
	Special electrode materials	Wide shielding trials	Geometrical and electric asymmetry	No shielding construction	EMC Class B solution
Activity	Extended DC experiments	Extended biophysical studies	Preparation of the ISO	Solve EMC immunity	Large-scale applications
	Pathological studies	Extended electrode studies, asymmetries	Preparation of the CE/MDD	Solve EMC interference	Complete production renewal
	Clinical probe-preparation	Clinical application	Systemic EHY-reconstruction	Complex safety	Bio electromagnetic development

One of the needs was for wide distribution to show popularly that hyperthermia depends on the device which delivers the heat. The heat delivery determines the efficacy and the selectivity could have completely different effects in the living tissue even when the measured overall temperature is equal with others. Some popular explanations were collected explaining the differences by the everyday experiences:

- All cars have four wheels and one steering-wheel. It does not mean that all the cars are equally good.
- All the cars have a fuel-consumption, but it does not mean that the best is which consumes the most.
- All the car-makers produce cars, but the experienced produce better ones.
- Every car can have an accident, but the safer offers better end.
- Every car has to be regularly checked for safety and proper performance, this is the basic of the optimal work.
- Your car is your everyday tool, naturally you need the best tool for your good job.
- Taking risk with the compromise in safety and performance you could lose your clients, your reliability and your job.

The technical development

One of the clues of the oncothermia technics is the construction of the electrode. Its geometry, material and construction is especially devoted to the task of impedance coupling. My Father said from the beginning: “oncothermia starts at their electrodes, the specialized solutions of electronics are supportive only”. The first application was the symmetric coupling of the field (flat electrodes).

Special bio-compatible and accurately chosen complex dielectric function rubber-coating were on the flat electrodes. These were acting symmetrically, but their control and optimizing of their efficacy was very difficult, and the accuracy was very much limited.

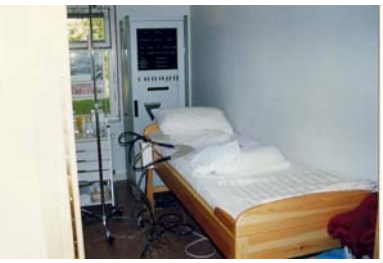
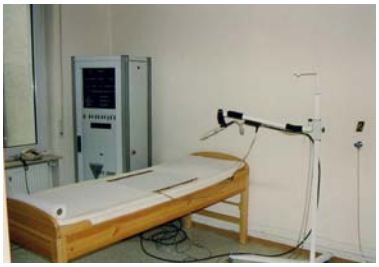

These electrodes were produced massively, but we learned that the accurate focusing (selection of the malignant cells) cannot be solved by symmetric solution.

Introducing asymmetry

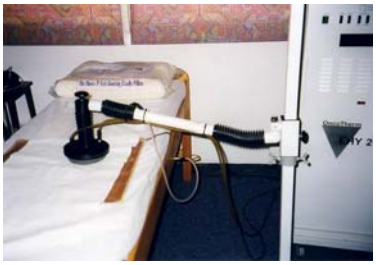

To introduce the asymmetry was a revolutionary step of the preciosity and efficacy of the treatment.


Some experiments were made on air-cooling as well, but its high sensitivity and base wave-transmission killed the idea. Helping the accuracy we used full-wooden furniture, the bed did not have a piece of metal.

Coupling of the field (Electrodes & applicators)

Symmetric solution Introducing geometrical asymmetry

The flat water-bolus and the flexible, contour-adjusting bolus were the evolutionary steps.

Electrodes and systems for different applications

Electrode holder beside the bed

Preparation of flat-bolus electrodes

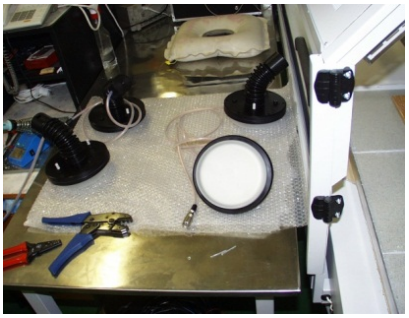
The symmetric head electrode

Preparation of the matrix-electrode

Electrode holder with the cooling unit

Numerous experiments were made on phantoms as well as on ourselves too.


The final asymmetric solution was experimentally well established and electronically balanced.

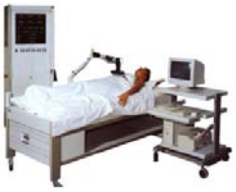





The head-phone like electrode was the last symmetric solution. This was problematic to control and was not an efficient solution, so all kinds of symmetric solutions were brushed aside.

Final trick: ASYMMETRIC electrode-solution

No wooden bed, no special conditions: high efficacy and selectivity, high safety and proper control. This is the ultimate technical solution of our 17 years' experience.

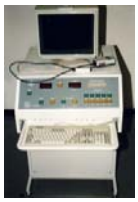



Development of the various groups of devices

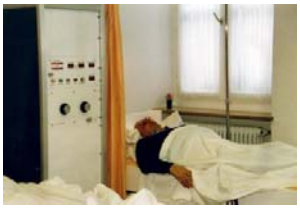
Oncothermia had changed the paradigm to break the stalemate situation of the hyperthermia applications in oncology.

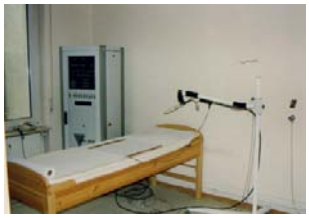
First steps (1988-1990) ECT systems, working on galvano effect, modified Nordenstrom's idea. The modification is the integration of the time-fractal fluctuations (fractal physiology approach). The devices were successfully applied. It had its first GS-sign certificate from TÜV.



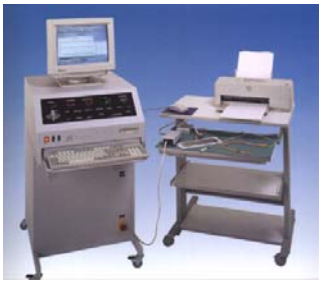

Basic synergy steps (1990-1993) EHY systems, uniting the loco regional hyperthermia with the ECT therapeutic modality. This device was the first hyperthermia device which received the CE mark from TÜV Münich. (Other auditor did not take the task thinking that it does not meet with the possible CE standards.)



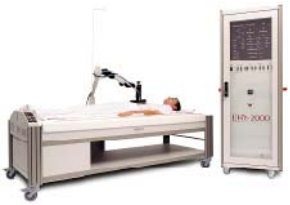



Extreme approach (whole body hyperthermia) (moderate and extreme infrared heating including the fractal modulation on 960 nm radiation) Oncotherm terminated this project, and tried to have alliance with other producers in this product.

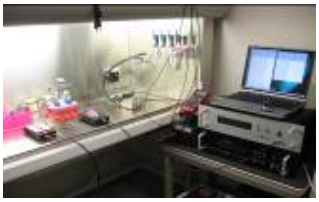
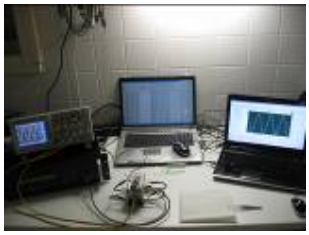
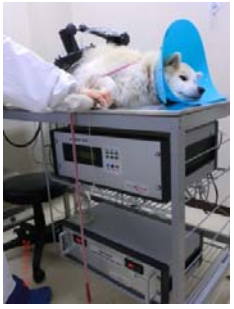

Intraluminar applications (PCT systems) Applied mainly for prostate treatment, including also the first application for benign tumors by oncothermia.

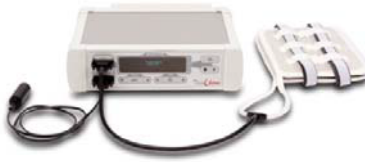
Modern oncothermia working in wide range of applications - It can be applied in cases when other therapies fail. It is the flag-ship device category, used in many hospitals and clinics worldwide.

The new systems target the research. The in-vitro and in-vivo applications together with the preclinical (veterinarian) research make oncothermia very unique on the market. The high-preciosity RF-specialized temperature measuring unit is also an Oncotherm product.


Based on the research new treatment lines are developed. The intraluminar (EHY1000 series) device is one of the successful products of the company. The Booster and the Androtherm devices are in clinical research study phase presently.




Special accessories are developed to help the treatment. The hand-held temperature measurement will be a regular accessory for the EHY devices, while the touch-screen technology is for upgrade facilities. The phantom is used for precise calibration of the devices by the accurate treatment, while the web-box is able to connect the device to the internet. A new in-vitro applicator is also developed.

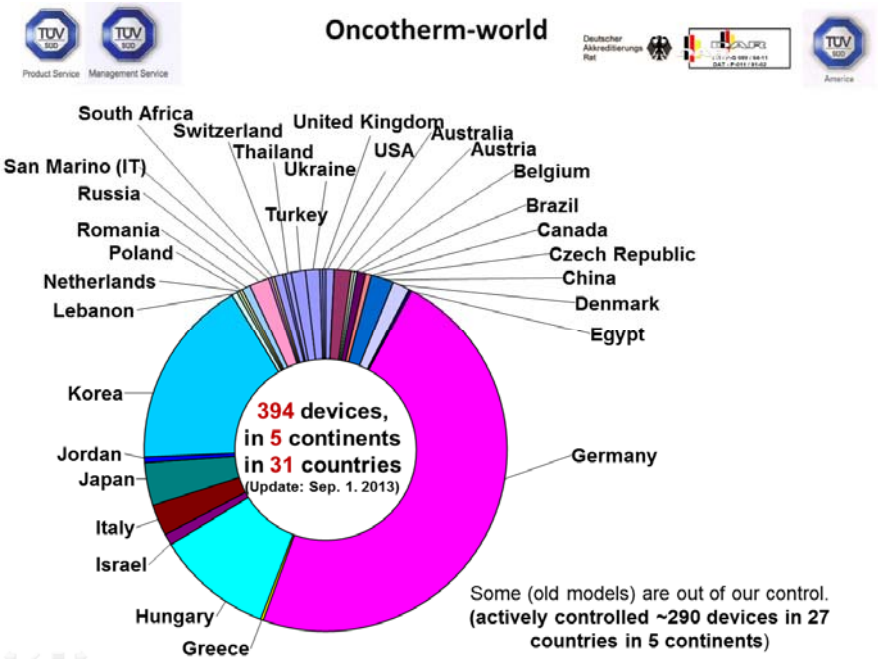




Production line and production team of Oncotherm devices in Toyama, Japan

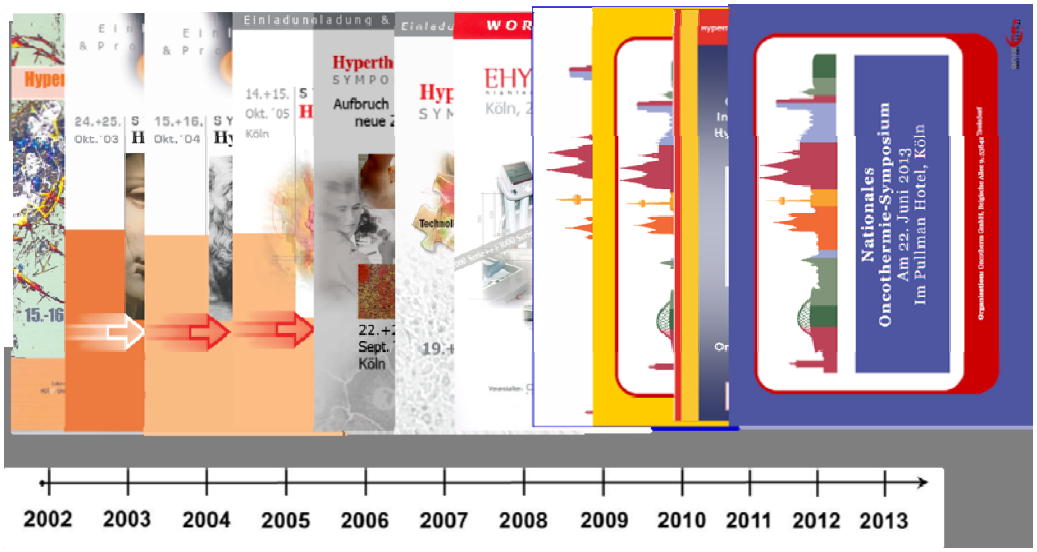
Oncotherm's presence in the world

These results base the spread of oncothermia worldwide, represented in 30 countries on five continents.



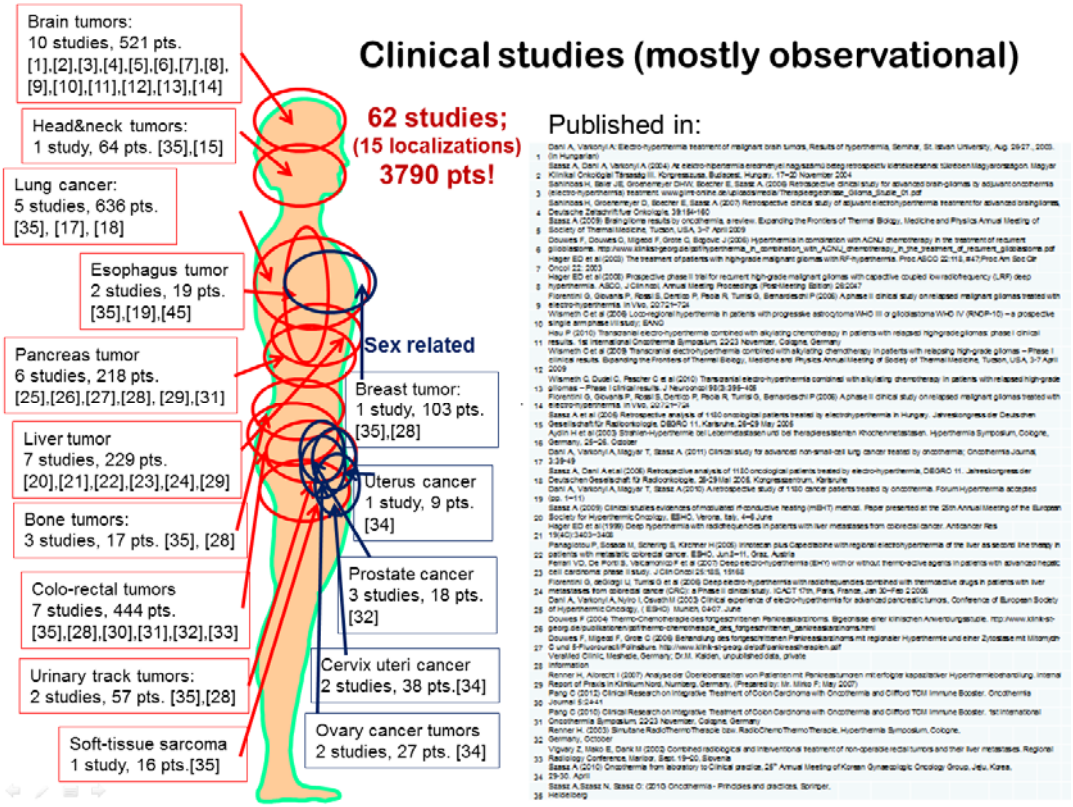
The method and the devices certified everywhere.

Oncotherm regularly organizes conferences for oncothermia users.



Users and researchers of oncothermia publish massively in the professional literature.

Numerous clinical studies were performed with oncothermia method.



Presently also numerous clinical studies (university locations with ethical approval) are in progress.

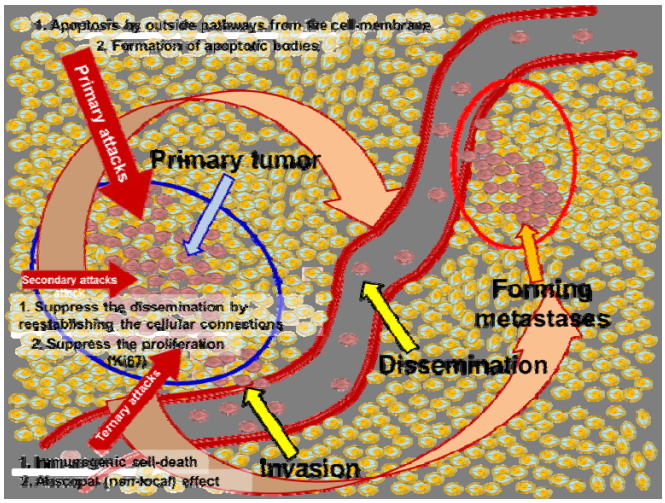
8	Continued studies	
1	MammaTherm Advanced Breast cancer)	LM Universitry Munich, Germany
2	TCM + Oncothermia	Clifford Hospital, China
3	AndroTherm – Peyronie disease	Italian Andrology Institute, Italy
4	OvaTherm (Advanced Ovarian cancer)	National Cancer Institute, South Korea
5	CervoTherm (Advanced Cervix cancer + HIV infection)	Johannesburg University, S. Africa
6	EsoTherm (Advanced Esophagus cancer + immune stimuli)	Chiba University, Japan
7	PancroTherm (advanced pancreas with liver meta)	Thai National Cancer Institute, Bangkok
8	BreastTherm (advanced breast cancer)	Thai National Cancer Institute, Bangkok

The experimental research is extendedly made worldwide.

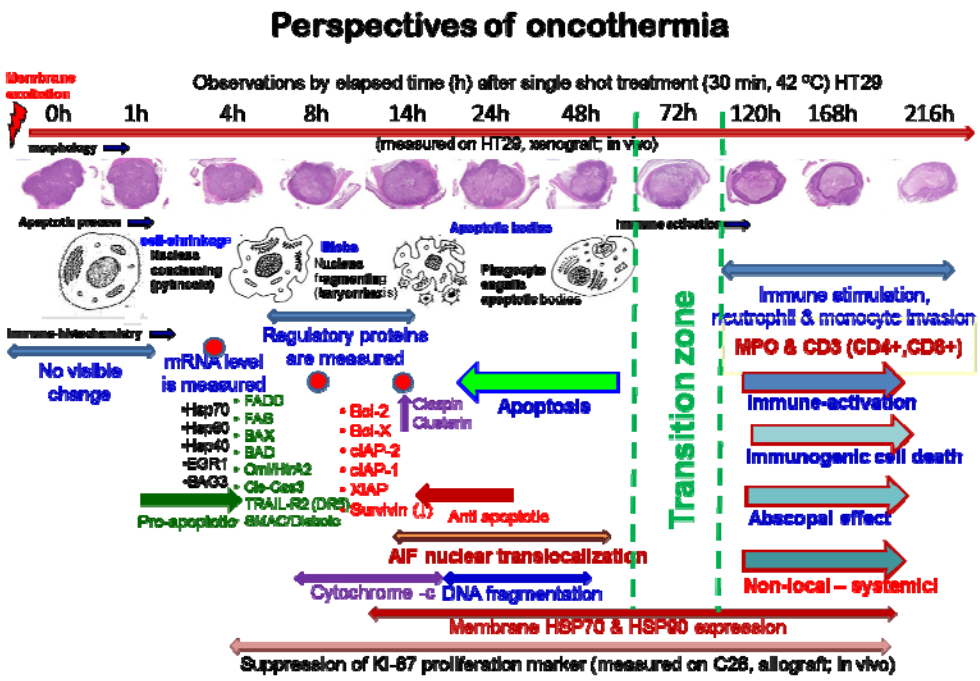
16	Experimental/Preclinical studies	
1	Immunoeffects (in vivo)	Semmelweis University, Hungary
2	Bystander effects (in vivo)	St.Istvan University (Veterinarian), Hungary
3	Dendritic cell effects	Chiba University, Japan
4	RF-vaccinantion study	St. Istvan University, Hungary
5	Veterianrian studies (dogs, cats)	Tottori University, Japan
6	Selective cell-distrotion mechanisms (in vitro)	Semmelweis University, Hungary
7	Electromagnetic effects (in vitro)	St.Istvan University (Veterinarian), Hungary
8	Correlation (entropy) effects (in silico)	Oncotherm laboratory, Hungary
9	Electric field distribution effects (in silico)	Pazmany P. Catholic University, Hungary
10	Viral effects (in vivo)	Oncotherm laboratory, Hungary
11	Ecciniococcus study (in vivo)	Dusseldorf University, Germany
12	Ecciniococcus study (in vivo)	Tottori University, Japan
13	Temperature distribution phantom models	Oncotherm laboratory, Hungary
14	TCM synergy with oncothermia	Oncotherm laboratory
15	Ultrasound apoptotic measurements	Pazmany P. Chatolic University
16	Fractal-template research	Oncotherm laboratory, Hungary

The future …

Oncotherm is a local treatment, but focuses its effect systemically as the malignant diseases request it. The main effect is the selective promotion of the apoptosis of malignant cells with external pathway excitations. This process is together with the damage associated molecular patterns forms immunogenic cell-death. In consequence, the apoptotic bodies carry the information for phagocytosis, and the immunogenic cell death together are able to perform immune recognition of the cancer, and act far from the local treatment. This is the abscopal effect, which is in the center of the present oncothermia research. Oncothermia acts on this way not only on the local tumor, but blocks the invasion and dissemination of malignant cells, as well as suppresses forming micro and macro metastases.



The perspectives of these treatments are in the immune-effects, and the patented tumor-vaccination.



Conclusion

Oncothermia is a feasible and well proven method for natural cell-killing and for immune activation as well. The new scientific developments devote to this method to be the fourth column of the gold-standard applications in oncotherapies.

References

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

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

[3] Roussakow S (2013) The history of hyperthermia rise and decline, Proceedings paper oft h 31st International Congress of the Hyperthemira Society, Volume 2013 (2013), Article ID 428027, http://www.hindawi.com/cpis/medicine/2013/428027/

[4] Maguire PD, Samulski TV, Prosnitz LR, Jones EL, Rosner GL, Powers B, Layfield LW, Brizel DM, Scully SP, Harrelson JM, Dewhirst MW. (2001) A phase II trial testing the thermal dose parameter CEM43 degrees T90 as a predictor of response in soft tissue sarcomas treated with pre-operative thermoradiotherapy, Int J Hyperthermia. 17(4):283-90

[5] Maarten de Bruijne, Bronno van der Holt, Gerard C. van Rhoon, Jacoba van der Zee (2010) Evaluation of CEM43 CT90 Thermal Dose in Superficial Hyperthermia, A Retrospective Analysis; Strahlen. Oncology, 186(8):436-43

[6] Roussakow S. (2013) Critical Analysis of Electromagnetic Hyperthermia Randomized Trials: Dubious Effect and Multiple Biases, Conference Papers in Medicine, Article ID 412186, 31 pages http://dx.doi.org/10.1155/2013/412186

[7] Storm FK (1993) What happened to hyperthermia and what is its current status in cancer treatment? J Surg Oncol 53:141-143

[8] Heiden MGV, Cantley LC, Thompson CB (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. Science 324(5930):1029-1033

[9] Szentgyorgyi A. (1968) Bioelectronics: a study in cellular regulations, defense and cancer, Academic Press, NY

[10] Schwan, H.P.: Electrical properties of tissue and cell suspensions. Adv. Biol. Med. Phys. 5, 147-209 (1957); Schwan, H.P.: Determination of biological impedances. In: Physical Techniques in Biological Research, vol. 6, pp 323-406, Academic Press, New York (1963); Schwan HP (1938) Biophysics of the interaction of electromagnetic energy with cells and membranes. In Grandolfo M, Michaelson SM, Rindi A (eds) Biological Effects and Dosimetry of Nonionizing Radiation. Plenum Press, New York, pp 213-231; Schwan HP (1982) Nonthermal cellular effects of electromagnetic fields: ac-field induced ponderomotoric forces. Br J Cancer 45(5):220-224

[11] Bassingthwaighte JB, Leibovitch LS, West BJ (1994) Fractal Physiology. Oxford Univ. Press, New York, Oxford

[12] Szasz A (2013) Challenges and solutions in oncological hyperthermia, Thermal Med, 29(1):1-23

[13] Hegyi G, Szigeti GP, Szasz A (2013) Hyperthermia versus Oncothermia: Cellular Effects in Complementary Cancer Therapy, Evidence-Based Complementary and Alternative Medicine, Article ID 672873, 12 pages, http://dx.doi.org/10.1155/2013/672873
[14] Szasz O, Szasz A (2013) Essentials of oncothermia, Conference Papers in Medicine, Article ID 159570, 20 pages, http://dx.doi.org/10.1155/2013/159570
[15] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology, 22:103-115
[16] Szasz A, Szasz O, Szasz N (2006) Physical Background and Technical Realization of Hyperthermia. In: Baronzio GF, Hager ED (2006) Hyperthermia in Cancer Treatment: A Primer, Springer Verlag, Landes Bioscience
[17] Szasz O, Andocs G. Meggyeshazi N (2013), Modulation Effect in Oncothermia, Conference Papers in Medicine Article ID 398678, 5 pages; http://dx.doi.org/10.1155/2013/398678
[18] Vincze G, Szasz N, Szasz A. (2005), On the thermal noise limit of cellular membranes. Bioelectromagnetics 26:28–35
[19] Andocs G, Renner H, Balogh L et al (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model. Strahlentherapie und Onkologie 185:120-126
[20] Vincze Gy, Szasz A (2006) Dose concept of oncological hyperthermia: Heat-equation considering the cell destruction, J Cancer Res Ther, Vol. 2, Issue 4, pp. 171-181
[21] Szasz A (2007) Hyperthermia, a modality in the wings, Journal of Cancer research and therapeutics 3:56-66
[22] Meggyeshazi N, Andocs G, Krenacs T. Programmed cell death induced by modulated electro-hyperthermia, Conference papers in Medicine (in press) http://www.hindawi.com/cpis/medicine/aip/187835/
[23] Meggyesházi N. Andócs G, Spisák S. Krenács T. (2013) Early Changes in mRNA and Protein Expression Related to Cancer Treatment by Modulated Electrohyperthermia; Conference Papers in Medicine; Article ID 249563, 3 pages, http://dx.doi.org/10.1155/2013/249563
[24] Meggyeshazi N, Andocs G, Szasz A (2011) Possible immune-reactions with oncothermia. ESHO, Aarhus, Denmark, May 26-28.(award winning presentation)
[25] Andocs G. Meggyeshazi N, Okamoto Y. Balogh L. Szasz O, (2013) Bystander Effect of Oncothermia, Conference Papers in Medicine, Article ID 953482, 6 pages, http://dx.doi.org/10.1155/2013/953482
[26] Andocs G, Szasz O, Szasz A (2009) Oncothermia Treatment of Cancer: From the laboratory to clinic, Electromagnetic Biology and Medicine, 28:148-165
[27] Andocs G, Okamoto Y, Kawamoto K, Osaki T, Tsuka T, Imagawa T, Minami S, Balogh L, Meggyeshazi N, Szasz O; (2013) Oncothermia Basic Research at In Vivo Level: The First Results in Japan, Conference Papers in Medicine, Article ID 197328, 6 pages, http://dx.doi.org/10.1155/2013/197328
[28] Andocs G, Okamoto Y, Osaki T, Tsuka T, Imagawa T, Minami S, Balogh L, Meggyeshazi N, Szasz O; (2013) Oncothermia Research at Preclinical Level, Conference Papers in Medicine, Article ID 272467, 9 pages, http://dx.doi.org/10.1155/2013/272467
[29] Szasz A, Szasz O, Szasz N (2013) Local hyperthermia in oncology, a chapter in book: Hyperthermia, ed. Huilgol N, ISBN 980-953-307-019-8 InTech
[30] Lee Youngsuk (2013) Oncothermia Application for Various Malignant Diseases, Conference Papers in Medicine, Article ID 245156, 6 pages, http://dx.doi.org/10.1155/2013/245156
[31] Szasz O, (2013) Burden of Oncothermia: Why Is It Special? Conference Papers in Medicine, Article ID 938689, 6 pages, http://dx.doi.org/10.1155/2013/938689
[32] Meggyeshazi N, Andocs G, Spisak S, Kiszner G, Balla P, Balogh L, Krenacs T (2012) Modulated electrohyperthemia causes caspase independent programmed cell death in HT29 colon cancer xenografts. Virchows Archiv Volume 463, Issue 2 , pp 329, Sept. 2012
[33] Hegyi G, Vincze G, Szasz A, (2012) On the dynamic equilibrium in homeostasis, Open Journal of Biophysics, 2:64-71
[34] Szasz O, Andocs G, Meggyeshazi N, (2013) Oncothermia as Personalized Treatment Option, Conference Papers in Medicine, Article ID 941364, 6 pages, http://dx.doi.org/10.1155/2013/941364
[35] Sahinbas H, Groenemeyer D, Boecher E, Szasz A (2007) Retrospective clinical study of adjuvant electrohyperthermia treatment for advanced braingliomas, Deutsche Zeitschrift fuer Onkologie, 39:154-160
[36] Tae Sig Jeung, Sun Young Ma, Jesang Yu, Sangwook Lim (2013) Cases That Respond to Oncothermia Monotherapy, Conference Papers in Medicine, Article ID 392480, 12 pages, http://dx.doi.org/10.1155/2013/392480