

Oncothermia – Nano-Heating Paradigm

Oliver Szasz* and Andras Szasz

Biotechnics Department, St. Istvan University, Hungary

Abstract

To face the challenges in hyperthermic oncology we have made research on nano-heating the malignant and healthy cells and this review paper shows our results which were presented at the largest OMICS Group Conference in the United States in 2013. We introduced nano-heating technology which means selecting and heating the membrane of the malignant cells purely by the electromagnetic effects without any extra nano-particle applications. The technology (called modulated electrothermia or oncothermia) is impedance controlled capacitive coupling; no plane-wave radiation is dominating as in other capacitive (radiative) solutions. The nano-selection is based on the metabolic, on the adherent and on the organizing deviations of the malignant cells from their healthy hosts. The cell-killing mechanism is connected to the intensive, but very local, nano-range heating. These effects are proven *in silico*, *in vitro* and *in vivo* experiments, as well as in pre-clinical and veterinarian applications. Based on the controllable and safe methodology the treatment is applied in human clinical practice. My objective is to summarize the results which are connected with oncothermia method.

Keywords: Nano-heating; Oncothermia; Apoptosis; Abscopal effect; Immune activation; Electromagnetic heating

Introduction

Hyperthermia in oncology is a typical scientific see-saw. Despite its privilege as the very first oncological therapy in human medicine, it is not accepted in the clinical practice as a daily routine. Its development was an almost unbroken success-story at the start when the effects were also directly connected to various religious beliefs, venerating the Sun and the radiated heat/fire as overall force in nature. The popular medicine of heat has been introduced to the households, and even today it is one of the most frequently applied home-cure for various diseases. However, the medical profession needs more efficacy and explanations too. Soon, it was realized in the middle ages that there are some shortcomings of hyperthermia in oncology, which were believed to be the consequence of the technological limits, such as the lack of deep-heating technology and proper safety control. More and more doubts were formulated and the method was rejected among the professionals until the discovery of electromagnetic heat-delivery. These kind of technical solutions were promising; they were used to deliver deep and accurately focused energy to fulfill the requirements of the classical thoughts about the healing values of high temperatures. A funny situation occurred: on the basis of the ancient knowledge, a relatively new and powerful technology, the “modern in time” electromagnetic heating started to be applied believing the accurate heat delivery can heal patients. There are numerous results showing the significant effects of this classical hyperthermia approach in oncology. Then, the basic explanation was the larger heat-sensibility of the cancer than that of the healthy tissue. The technology has been developing fast to fulfill the demands:

- Good heating techniques has been developed
- Powerful energy-delivery has been realized
- Various solutions to focus the energy in depth has been solved
- Numerous high-ranked research institutes have been included in the intensive research
- Some excellent clinical trials have been performed

What else was necessary to make the overall acceptance common in oncology? The reproducibility of the results, the dosing for control

and the deep understanding of the effects were missing. Unfortunately, the general strategic goal of the treatment also lost its original direction. The classical hyperthermia substituted the goal of cure with the tool, requesting higher and higher local temperatures instead of optimizing the effects. The strategic disorientation is even deeper to see how classical hyperthermia concentrates on the local tumor instead of the patient who has the tumor. Furthermore, this loss of medical orientation caused a real mistake too: regarding the tumor as local disease, but the cancer is only apparently that local tumor; it is malignant, which definitively has systemic effect; only the benign tumor would be local. The discrepancy of the non-locality of the tumor and the local treatment is a central problem in case of hyperthermia, because the patients are treated with this method in higher lines only. The “gold standards” have some advantages; those are applied first of course. Despite the tremendous number of books published on hyperthermia in oncology, [1-20] the complete history of oncological hyperthermia was fluctuating between the “beliefs” and “disbeliefs” (Figure 1), the success and failures [21].

The problems have obvious reasons (Figure 2) [22]:

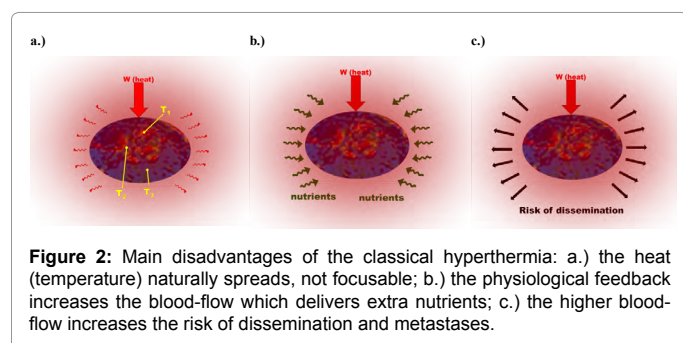
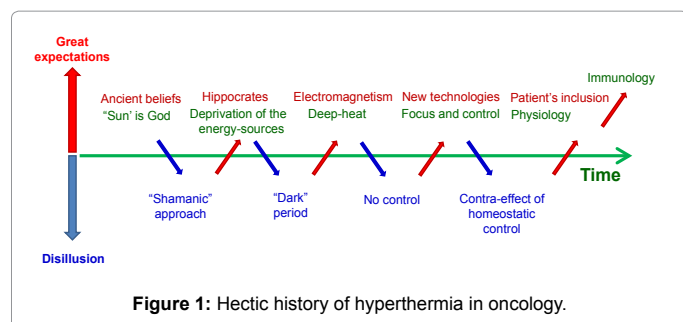
- The focus of energy does not mean the focus of the temperature. The temperature (and the heat to what the absorbed energy is converted) naturally spreads all over the neighborhood until the thermal equilibrium.
- The temperature and the heat energy are not simply correlated, because the equally heated volume has no equal cooling by heat-conduction and heat-convection. Here, the heat convection (the various change of the blood-flow which cools down the volume) has the largest modification factor.

***Corresponding author:** Oliver Szasz, Associate Professor, Biotechnics Department, St. Istvan University, Oncotherm Kft. Ibolya u. 2. 2071 Páty, Hungary, Tel: +36 (23) 555 510; Fax: +36 (23) 555 515; E-mail: biotech@gek.szie.hu

Received January 24, 2014; **Accepted** March 26, 2014; **Published** March 31, 2014

Citation: Szasz O, Szasz A (2014) Oncothermia – Nano-Heating Paradigm. J Cancer Sci Ther 6: 117-121. doi: [10.4172/1948-5956.1000259](https://doi.org/10.4172/1948-5956.1000259)

Copyright: © 2014 Szasz O, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



- The growing temperature gains the homeostatic feedback, which tries to equalize the constrained temperature increase. This is made by increased blood-flow, which delivers nutrients supply the tumor
- The higher blood-flow increases the risk invasion, of dissemination and of distant metastases.

Due to the precariousness of the comparisons, many prospective clinical trials of conventional hyperthermia are questioned [23]. "Reference point is needed" as formulated clearly in the literature [24]. The definition of dosing has to be fixed for a future development of hyperthermia [25]. An important message was formulated a long time ago [26]: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment."

Method-Nano-Heating Technology

The definite aim is not to heat-up the targeted volume. This heating up is only a tool, to lead us to the real goal: destroy and eliminate the malignant cells. The tumor is a complex structure, having various compartments, and only a part of it contains tumorous cells -, which have to be our only targets. Why are we forced to heat up the complete target? We have to heat the malignant cells, and add energy only where it is necessary to destroy the malignant cell. This is the membrane, which we have to target and modify. If we are able to target the cellular membrane of the malignant cells only, then we can reach our goal without heating up the whole tumor gaining the unwanted physiological feedback by the increase of the blood-flow.

For the new paradigm we have to bear in mind these three definite points:

- (1) Accurate selection of malignant cells
- (2) Avoid gaining the blood-flow
- (3) Use effective cell-killing,

These are interconnected when we choose the very local pointing of the energy liberation. In this case the concentrated energy heats up and excites the malignant cells, but does not heat up the complete tissue to avoid the negative feedback of the homeostatic control. This construction will automatically avoid the sudden increase of the blood-flow in the heated target. This method is the modulated electro-hyperthermia (oncothermia) [27].

The accurate selection of malignant cells is a key step in the proper oncothermia. There are robust electromagnetic differences between the malignant and healthy cells *in vivo*. The biological processes and structures of the healthy cells are distinguishably different from the malignant ones. These differences make it possible to accurately select the cancer-cells by their electromagnetic behaviors and actively destroy them without damages to their healthy neighborhood [28].

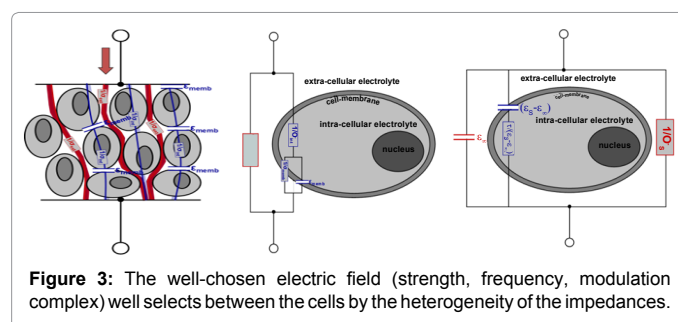
The thermal effect itself is important, but has to be limited to the very local "points" which are most sensitive to any lethal attack on the malignant cells. The first is the well-chosen radiofrequency current [29], which constructs thermal gradient between extra- and intra-cellular electrolytes, Figure 3. The applied 13.56 MHz carrier frequency with proper time-fractal modulated current [30] is essential to have proper effect. (Its technical description can be found elsewhere [31].) This gradient could be the driving force of the of the membrane excitation for signal propagation. These effects are thermal, but not temperature dependent [32,33], they depend on the temperature differences through the membrane, and act like the usual first order phase transition with latent energy exchange at constant (transition) temperature.

The proper attack has to be localized on the cell-membrane of the malignant cells, which uses the specialty of the metabolic rate of the malignant cells (Warburg effect [34]). For this pointing oncothermia uses the differences in the dielectric constant of the extracellular electrolyte and membrane-bound water of the malignant and healthy cells (Szent-Gyorgyi effect [35]; combined with β (8) dispersion, Schwan effect [36]). A special spatio-temporal fluctuation characterizes the homeostatic equilibrium [37]. A new approach of the living state has been developed: the fractal physiology [38]. In the living system, instead of the deterministic actions, stochastic processes occur, so the predictions always have random, unpredictable elements. Considering these the applied modulation in oncothermia [39] helps to localize the malignancy in a complex target [40] (Figure 4).

The effects of the above mentioned selective actions complexly complete each other as shown in Figure 5 [41].

Results

The synergy of electric field with the thermal effects has more efficacy than the conventional hyperthermia has [42]. The temperature



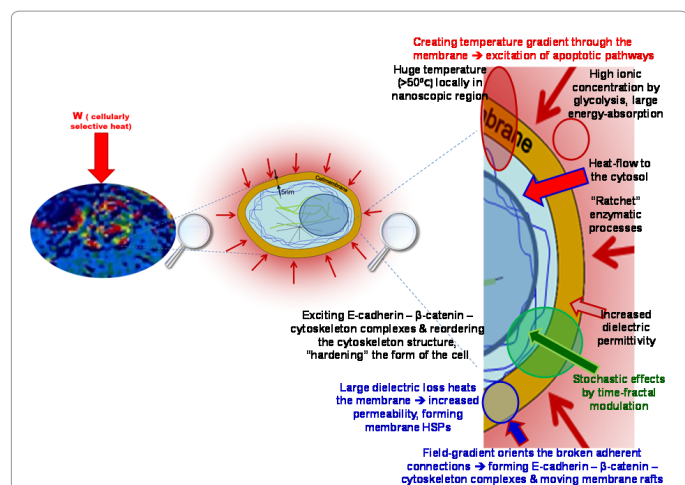


Figure 4: The nano-heating acts at the membrane of malignant cell, and does not heat up the complete tissue, it avoids the physiological feedback of the increased blood-flow.

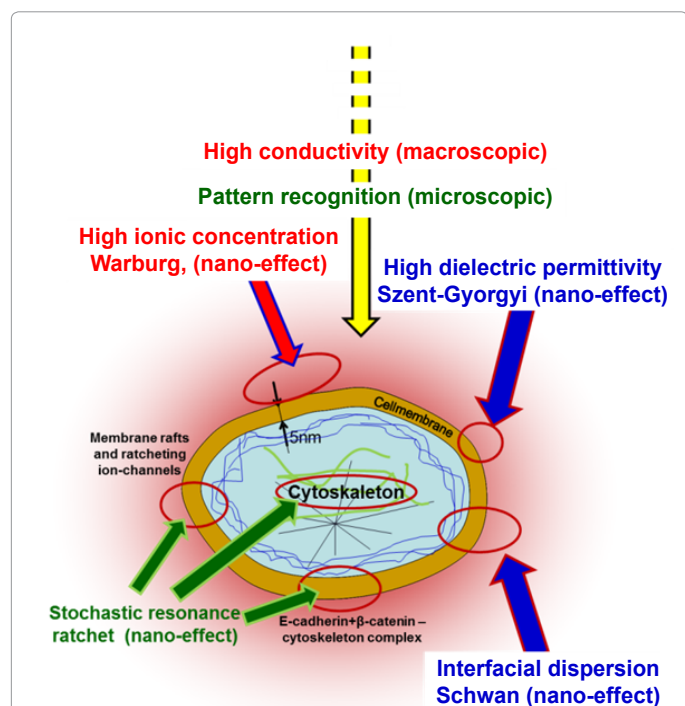


Figure 5: The well-chosen electric field (strength, frequency, modulation complex) well selects between the cells by the heterogeneity of the impedances.

gradient changes the membrane processes and promotes signal pathways for natural apoptosis [43], instead of the thermal necrosis. Temperatures above 41-42°C produce substantial cellular damage [44].

The apoptotic cell-death and any systemic immune-action following it would be more natural than the necrosis which is the standard goal of the classical hyperthermia dosing the complete problem by the necrotic standard (CEM43°C). The apparent contradiction of conventional hyperthermia is solved by oncothermia, having high temperature on the cellular membrane but in average on a larger volume the complete temperature remains under the limit helping the immuno-effective

processes, which need the average temperature to remain under 40°C limit [45].

In oncothermia applications the apoptosis becomes robust after 24 h [46]. The complete time course studies clearly show the details of the apoptotic process [47]; which is measured histochemically with various methods. Measurements in time-course very clearly show the development of the natural apoptotic processes in xenograft model (*in vivo*, HT29, Figure 6) [48,49]. It is important that after the apoptosis, a special invasion ring was formed around the treated tumor and the neutrophil and monocytes activity were measured in the region indicating immune activation of oncothermia process. The expression of CD3, CD4 and CD8 gave enough information expecting certain abscopal (bystander) effect by local oncothermia [50]. Massive apoptotic signal-transduction starts from the membrane by the electric excitation [51], which is well proven, in mRNA level too [52]. The important results are the possible immune effects of oncothermia, which could lead to a systemic action too [46].

The time delay indicates the long-duration processes, which were identified as programmed cell-death (apoptosis), by various investigations: macro- and micro-morphology, enhanced activity of p53 tumor-suppressor, cleaved caspase 3 involvement, TUNEL reaction, DNA fragmentation (laddering), etc. were carefully measured [53]. Massive presence of apoptotic bodies can also be observed together with the typical TUNEL reaction.

Despite the fact that oncothermia is a local treatment, it acts systemically, Figure 7. Oncothermia suppresses the proliferation rate in the remaining living part of the treated tumor too. A measurement was provided by Ki67 proliferation marker, [54]). The surviving, living malignant cells in the treated tumor definitely and significantly suppressed the Ki67 marker compared to its untreated counterpart in all the investigated time-scales. Together with the certain suppression of the proliferation, the adherent connections are reestablished [55] blocking the disseminative processes. New connections make the

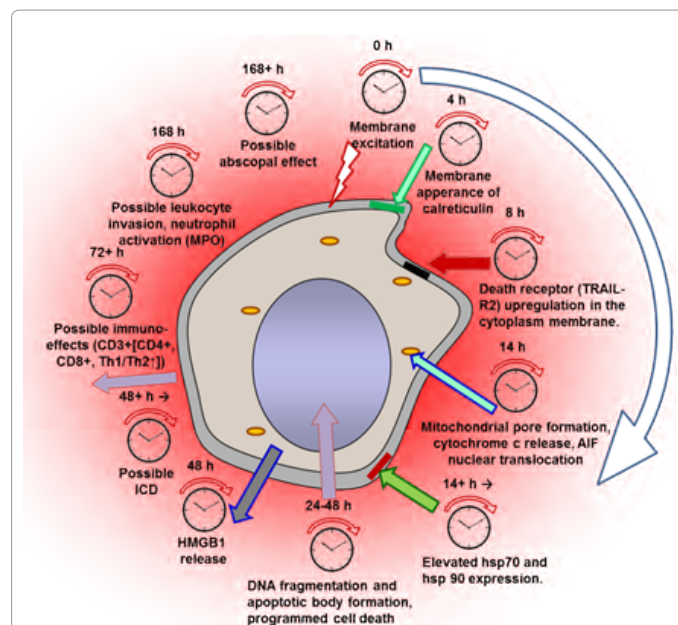
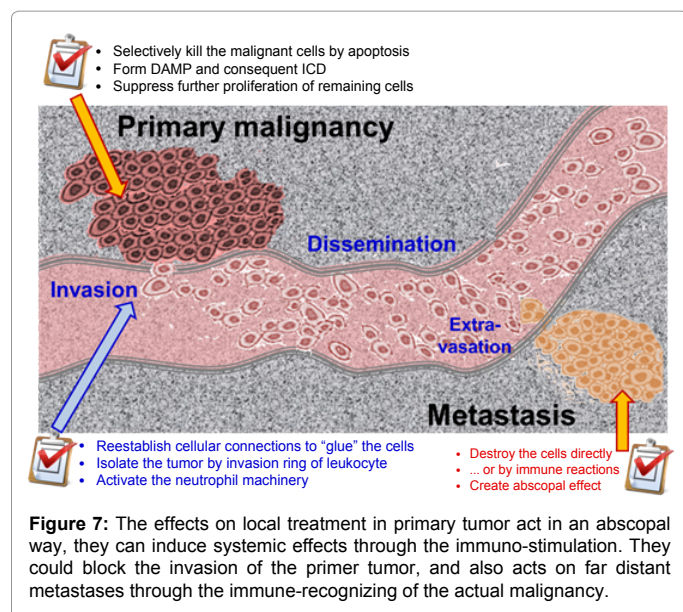


Figure 6: The well selected membrane excitation initializes a set of special bio-molecular effects to kill the cell and produce recognition of the malignancy by the immune-system.



missing signal-transmissions possible too. An important observation was the reestablishment of the E-cadherin bonds between the cells [46], well forming a complex with the β -catenin for signal transduction. This cell-cell connection is not only an effective signal transmitter, but it well blocks the cellular dissemination by fixing the malignant cells in tight connective way.

The research results are well applied in the treatment practices being followed from the laboratory to the clinical bed, showing proofs of the above principles [55]. The veterinarian, pre-clinical level [49] together with wide range of clinical studies and practical clinical applications show the feasibility of oncothermia [26,46,56-60] as a complementary treatment to multiply other conventional oncotherapies. Its application as a monotherapy, when other treatments fail, is also promising [61].

Conclusion

Oncothermia shows its definite advantages in local cell-killing and in blocking the metastatic processes too. It is a feasible method to become the reliable and controllable basis of the modern hyperthermia demands in oncology.

Acknowledgement

This research was supported by numerous doctors and researchers who have been working on this concept for 20 years now, especially to the founder Prof. Dr. A. Szasz and also to Prof. Dr. G. Hegyi, Dr. G. Andocs, Dr. N. Meggyeshazi, Dr. Cs. Kovago, Dr. T. Krenacs and Dr. Gy. Szigeti.

Declaration of Interest

Author is presently CEO of Oncotherm company.

References

- (2013) 3rd World Congress on Cancer Science and Therapy in October 21-23, 2013 at Double Tree by Hilton Hotel San Francisco Airport, USA.
- Streffer C, Van Beuningen D, Dietzel F (1978) Cancer therapy by hyperthermia and radiation. Urban and Schwarzenberg, Baltimore-Munich.
- Hornback NB (1984) Hyperthermia and cancer: Human clinical trial experience. CRC Press, Boca Raton Florida.
- Gautherie M, Albert E (1982) Biomedical Thermology. (eds) Alan R. Liss, New York.

- Anghileri LJ, Robert J (1986) Hyperthermia in cancer treatment. CRC Press Inc, Boca Raton, Florida.
- Field SB, Franconi C (1987) Physics and technology of hyperthermia. NATO ASI series, Martinus Nijhoff Publ. (eds) Dordrecht, Boston.
- Urano M, Douple E (1989) Hyperthermia and Oncology. Thermal effects on cells and tissues. (eds) VSP BV, Utrecht, The Netherlands.
- Urano M, Douple E (1989) Hyperthermia and Oncology, Biology of thermal potentiation of radiotherapy. (eds) VSP BV Utrecht, The Netherlands.
- Gautherie M (1990) Methods of hyperthermia control. (ed) Springer Verlag, Berlin
- Gautherie M (1990) Biological Basis of oncological thermotherapy. (ed) Springer Verlag, Berlin
- Gautherie M (1990) Interstitial endocavitary and perfusional hyperthermia. (ed) Springer Verlag, Berlin
- Urano M, Douple E Hyperthermia and Oncology/Interstitial Hyperthermia: Physics, biology and clinical aspects. (eds) VSP BV, Utrecht, The Netherlands.
- Seegenschmiedt MH, Sauer R, Miyamoto C, Chalal JA, Brady LW (1993) Clinical experience with interstitial thermoradiotherapy for localized implantable pelvic tumors. Am J Clin Oncol 16: 210-222.
- Matsuda T (1993) Cancer treatment by hyperthermia, radiation and drugs. Taylor & Francis, (ed) London-Washington DC.
- Urano M, Douple E (1994) Hyperthermia and Oncology, Vol.4. Chemopotential by hyperthermia. VSP BV, Utrecht, The Netherlands
- Seegenschmiedt MH, Fessenden P, Vernon CC (1995) Thermoradiotherapy and Thermochemotherapy, Biology, physiology and physics. Springer Verlag, Berlin Heidelberg.
- Seegenschmiedt MH, Fessenden P, Vernon CC (1996) Thermo-radiotherapy and Thermo-chemotherapy, Clinical applications. Springer Verlag, Berlin Heidelberg.
- Kosaka M, Sugahara T, Schmidt KL, Simon EI (2001) Thermotherapy for Neoplasia, Inflammation, and Pain. Springer Verlag, Tokyo, pp-550.
- Ellis LM, Curley SA, Tanabe KK (2004) Radiofrequency ablation of cancer. Springer Verlag, New York, Berlin
- Baronzio GF, Hager ED (2006) Hyperthermia in Cancer Treatment: A Primer. Springer Verlag, Landes Bioscience.
- Roussakow S (2013) The history of hyperthermia rise and decline. Conference Papers in Medicine 2013: 1-40.
- Szasz A (2013) Quo-vadisA oncologic hyperthermia? Conference Papers in Medicine 2013: 1-15.
- Roussakow S (2013) Critical Analysis of Electromagnetic Hyperthermia Randomized Trials: Dubious Effect and Multiple Biases. Conference Papers in Medicine 2013: 1-31.
- Fatehi D, van der Zee J, van der Wal E, Van Wieringen WN, Van Rhoon GC (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.
- Jones E, Thrall D, Dewhirst MW, Vujaskovic Z (2006) Prospective thermal dosimetry: the key to hyperthermia's future. Int J Hyperthermia 22: 247-253.
- Storm FK (1993) What happened to hyperthermia and what is its current status in cancer treatment? J Surg Oncol 53: 141-143.
- Szasz A, Szasz N, Szasz O (2011) Oncothermia: Principles and Practices. Springer Verlag GmbH, Heidelberg: 565.
- Brunner G, Andocs G (2007) Electric hyperthermia of Skin cancers: New results on the potential molecular mechanisms of action. Hyperthermia Symposium.
- Szasz A, Szasz O, Szasz N (2001) Electro-hyperthermia: a new paradigm in cancer therapy. German Journal of Oncology 33: 91-99.
- Szasz O (2013) Burden of oncothermia: Why is it special? Conference Papers in Medicine 2013: 1-6.
- Szasz A, Szasz O, Szasz N (2006) Physical Background and Technical Realization of Hyperthermia. In: Baronzio GF, Hager ED. (eds.) Hyperthermia in Cancer Treatment: A Primer. Springer Verlag, Landes Bioscience, pp-33.

-
32. Szasz A, Vincze G (2006) Dose concept of oncological hyperthermia: heat-equation considering the cell destruction. *J Cancer Res Ther* 2: 171-181.
33. Szasz A (2007) Hyperthermia, a modality in the wings. *J Cancer Res Ther* 3: 56-66.
34. Warburg O (1966) *Oxygen, The Creator of Differentiation*, Biochemical Energetics, Academic Press, New York.
35. Szentgyorgyi A (1968) *Bioelectronics, A Study on Cellular Regulations, Defense and Cancer*. Academy Press, New York, London.
36. Schwan HP (1982) Nonthermal cellular effects of electromagnetic fields AC-field induced ponderomotive forces. *Br J Cancer Suppl* 5: 220-224.
37. Musha T, Sawada Y (1994) *Physics of the living state*. Amsterdam: IOS Press.
38. Bassingthwaite JB, Leibovitch LS, West BJ (1994) *Fractal Physiology*. Oxford Univ. Press, New York, Oxford.
39. Szasz O, Andocs G, Meggyeshazi N (2013) Modulation effect in oncothermia. *Conference Papers in Medicine* 2013: 1-5.
40. Szasz A (2013) Electromagnetic effects in nanoscale range in book *Cellular response to physical stress and therapeutic application*. Nova Science Publishers.
41. Szasz A, Vincze G, Szasz O, Szasz N (2003) An Energy Analysis of Extracellular Hyperthermia. *Electromagnetic Biology and Medicine* 22: 103-115.
42. Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, et al. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing. *Strahlenther Onkol* 185: 120-126.
43. Meggyeshazi N, Andocs G, Szasz A (2011) Possible immune-reactions with oncothermia. ESHO, Aarhus, Denmark.
44. Repasky E, Issels R (2002) Physiological consequences of hyperthermia: heat, heat shock proteins and the immune response. *Int J Hyperthermia* 18: 486-489.
45. Beachy SH, Repasky EA (2011) Toward establishment of temperature thresholds for immunological impact of heat exposure in humans. *Int J Hyperthermia* 27: 344-352.
46. Andocs G, Okamoto Y, Osaki T, Balogh L, Szasz O (2012) Bystander effect of oncothermia. *Conference Papers in Medicine* 2013: 1-6.
47. Meggyeshazi N, Andocs G, Balogh L (2013) Modulated electrohyperthermia induces DNA fragmentation and caspase independent programmed cell death in HT29 colorectal cancer xenografts. *Radiology and Oncology* (in press).
48. Andocs G, Okamoto Y, Kawamoto K, Osaki T, Tsuka T, et al. (2013) *Oncothermia Basic Research at In Vivo Level: The First Results in Japan*. *Conference Papers in Medicine* 2013: 1-6.
49. Andocs G, Osaki T, Tsuka T, Imagawa T, Minami S, et al. (2013) *Oncothermia Research at Preclinical Level*. *Conference Papers in Medicine* 2013: 1-9.
50. Andocs G, Meggyeshazi N, Galfi PBL, Fonyad L, Muller L, et al. (2010) Experimental oncothermia in nude mice xenograft tumor models. *Oncothermia a Journal* 17: 35-55.
51. Meggyeshazi N, Andocs G, Krenacs T (2013) Programmed cell death induced by modulated electro-hyperthermia. *Conference Papers in Medicine* 2013: 1-3.
52. Meggyeshazi N, Andocs G, Spisak S, Krenacs T (2013) Early Changes in mRNA and Protein Expression Related to Cancer Treatment by Modulated Electrohyperthermia. *Conference Papers in Medicine* 2013: 1-3.
53. Andocs G, Szasz O, Szasz A (2009) In vitro and in vivo evidences of effects of modulated rf-conducting heating. 25th Annual Meeting of the European Society for Hyperthermic Oncology, ESHO, Verona.
54. Szasz A, Szasz O, Szasz N (2013) Local hyperthermia in oncology, a chapter in book: *Hyperthermia*, ed. Huilgol N.
55. Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. *Electromagn Biol Med* 28: 148-165.
56. Doo Yun Lee, Seok Jin Haam, Tae Hoon Kim, Jae Yoon Lim, Eun Jung Kim, et al. (2013) Oncothermia with Chemotherapy in the patients with Small Cell Lung Cancer. *Conference Papers in Medicine* 2013: 1-7.
57. Szasz O, Andocs G, Meggyeshazi N (2013) Oncothermia as personalized treatment option 2013: 1-6.
58. Szasz A (2013) Clinical studies made by oncothermia, *Oncotherm Journal* 8.
59. Rubovszky G, Nagy T, Gödény M, Szász A, Láng I (2013) Successful treatment of solitary bone metastasis of non-small cell lung cancer with bevacizumab and hyperthermia. *Pathol Oncol Res* 19: 119-122.
60. Lee Y (2013) Oncothermia application for various malignant diseases, *Conference Papers in Medicine* 2013: 1-6.
61. Jeung TS, Ma SY, Lim S, Szasz A (2013) Cases that respond to oncothermia monotherapy. *Conference Papers in Medicine* 2013: 1-12.