Local Electro Hyperthermia in Cancer Therapy

Prof. Dr. habil A. Szasz, University Budapest, Hungary

Definitions and definitive actions

Hyperthermia is a rapidly developing treatment method in cancer- and tumor-therapy. HOT-OncoTherm is dealing with a new and highly effective hyperthermia method: **OncoThermia**. Conventional hyperthermia applies heat to achieve curative influence. The consequence of the regional overheating is the higher metabolism in the tumour-region. The expected effect was mainly to change the pH-environment of the malignant tissue by the elevated temperature based on the higher rate of metabolism, accompanied with the lack of the increased blood perfusion. The consequential oxygen deprivation and nutrient impoverishment will generate massive acidosis because of the anaerobic energy production. This mechanism denatures the enzymes and proteins in the tumor tissue. Anyway, the tumor cells are characterised by reduced thermo-regulation capability, allowing a significant instability by their overheating to unsettle the tumor from the state of equilibrium growth.
Starting from the alternative medicine methods used in ancient cultures, various procedures have been applied to deliver heat into the malignant area but the stable and calculable effect could not be completed.

Reduction effects and potentialization

1. The effect of oncothermia on the cancer tumours depends in general on the decreased thermo-regulation capability of tumours. The blood-vessels in the tumor tissue have insufficient wall structure, therefore they are not able to conform to the temperature changes. At the increase of temperature, the blood supply of tumor tissues decreases while that of healthy tissue increases. This is a certain selection to heat-treatment procedure: the healthy tissue temperature is regulated by the blood perfusion, while the tumor tissue could be effectively heated, without the thermo-regulation of the blood. The missing collectivity of the tumor tissue, its uncontrolled, relatively isolated growth works also against the heat equalisation.
2. As the metabolism of tumor tissues is more active than that of the healthy ones (their continuous proliferation requests a massive energy consumption), so their heat production is relatively high. Consequently, the tumor tissue is usually warmer than the healthy one. This additionally "trapped" heat enforces the tumor tissue to further increase their metabolism with a result of an additional increase of temperature. Consequently, this is a self-exciting, positive feedback process.
3. The outcome of the additional hyperthermia treatments will be the endothelium swelling and the micro-embolization, consequently, the weakening of blood flow, makes an angiogenetic blockage. This blockage stops the perfusion of the new agiogenetic capillary vessels and blocks the agiogensis as well.
4. However, there is not enough oxygen available for the increased metabolism; resulting in hypoxia and anaerobe metabolism and produces acidosis. The cell destructive effect of acidosis is well-known.
5. Furthermore, the increased metabolism significantly decreases the ATP content of cells, therefore their metabolism gets into a self-restrictive phase resulting in increased cell destruction.
6. The DNS replication can be blocked by means of heat effect slowing down the reproduction processes.
7. Hyperthermia significantly potentiates the chemo-therapy by increasing the drug-intake and drug metabolism, as well as the higher temperature allows extra pharmaco-kinetic effects by the higher chemical activities of the drugs.
8. Hyperthermia considerable potentiates the radio-therapy significantly gaining the Thermal Enhancement Ratio (TER).
9. Significant pain-reduction and the few side-effects are the specific advantages of hyperthermia. These facts may contribute to a considerable improvement of life quality.

10. Hyperthermia enhances the efficiency of the immune-reactions as well.

Hyperthermia Update Technique => OncoThermia

The delivered heat in the classical hyperthermia brings up some problems as well. The treatment temperature has been considered as the main technical parameter. Unfortunately, the heat-shock protein (HSP) synthesis may considerably suppress the cancer treatment's efficiency, adapting cells to survive the shock. OncoThermia (electro-hyperthermia) heats up the targeted tissue by means of electric field, producing less HSP-synthesis in the cells than a usual hyperthermia process. The main idea is to keep the energy absorption in the extracellular matrix (ECM). Heating the ECM, increases the ion-mobility, intensifies the metabolic rate of the cells, and destroys the cell membrane before the heat-shock activates the intra-cellular HSP mechanisms driven by the cell nuclei.
The hyperthermia method is one of the effective treatment methods in oncology, intensively active on clinical trials requested by the rules of the evidence based medicine. It is going to be a new modality of cancer treatments.
Hyperthermia update technique, the OncoThermia (electro-hyperthermia) is highly selective, gentle and safe, providing all the positive effects of the conventional hyperthermia with additional extra advantages. Its effectiveness is mainly based on the induced chaperone expression in the extra-cellular and suppressed shock-protein induction in intra-cellular region. Furthermore, the method induces the immune surveillance to attack the malignant cells by stimulus of HSP90-a in extra-cellular electrolyte. The OncoThermia extends the thermal treatment efficiency by non-thermal effects.

Historical notes

The history of heat-treatment in the therapy of certain diseases can be traced back to the year of 2400 B.C. At the age of the civilized culture of ancient Egypt the healers had applied photoactive vegetal extracts on the cancerous surface of skin and in the case of mammary cancer followed by sunlight treatment. Use of hyperthermia for cancer therapy has been documented for thousands of years. The first provable application was attributed to Hypocrites for the healing of breast tumour. His opinion based on the ancient Greek philosophy was: "If you are not able to heal the illness by medicine, you have to perform an operation. If this illness is not operable, you have to heal it by using heat. If this it is not curable by heat, there is nothing we can do."
In the Middle Ages various types of tumours had been treated by red-hot iron. This healing technique revived around the end of the last century when it was possible to solve the problem of deep penetrating energy transfer. The possibility of overheating with the purpose of enhancement the effect of radiation at malignant tumours had been first described in 1910.
In the struggle against infectious diseases the artificial fever (application of heat) plays an important role. Thus, two main application fields have been developed for thermotherapy:
active hyperthermia, where the high fever-shock is generated by applying intravenous portioning of pyrogenetic material.
passive hyperthermia, where the rise in the body temperature is induced by the insertion of device from outside.
The present situation of oncological hyperthermia is similar to that of the start of the radiology, when the ionising radiation was discovered: we know, this is a well applicable method, however, its exact dose, its contraindications and limits, the conditions of optimal treatment have not been clarified yet in details. Additional typical feature of hyperthermia as for any early-stage therapies is the lack of adequate treatment experience and long-range and comprehensive statistics.

Publications and conferences:

There are increasing number of the relevant published books and periodicals as well as a large number of scientific articles are published in high ranked, good impact factor journals. The increasing number of applications and clinical trials at universities, clinics, hospitals and institutes prove the feasibility and applicability of clinical hyperthermia in cancer therapies.

Scientific, medical and clinical situation

Some clinical trials are collected in the following Table:

Localization	Trial phase	Radio-dose [Gy]	Chemo	Response conventional alone [%]	Response with hyperthermia [%]	Number of patients
Head- and neck CA	Ph. I/II.	70-77	no		92	27
Head- and neck CA	Ph. III.	40		15	20	184
Malignant non-Hodgkin	Ph. III.			61	64	172
Recurrent Breast CA	Ph. III.					
Cervical CA	Ph. III	10.8	no	52.6	83.3	37
Cervical CA	Ph. III	High brachy	no	50	80	40
Esophagel CA				24.2	50.4	66
Malignant melanoma		27		28	46	70
Rectal CA	Ph. II.	45	yes		60	40
Gastric Tu		20		35.5	57.6	293
Breast CA (superf.)	Ph. III.		no	41	61	148
Glioblastoma mf.	Ph.II/III.	59.4	no	15	31	112
Soft tissue sarcoma	Ph II	No	yes			59
Superficially located CA	Ph II	Yes	no	62.6	82.8	92
Lung CA		No	yes			31
Nonsmall Lung CA		Yes	no	20	73	49
Esophagel CA		60		59	81.2	66
Bladder CA, Cervical CA, Rectal CA	Ph. III	65	no	39	55	358

OncoThermia: new paradigm in hyperthermia

There are considerable discussions on the relevant treatment parameters and optimisation of the treatment. Most of the physicians are convinced: the single important factor is the temperature itself. However, there are strong opposing opinions, which declare the delivered heat (absorbed energy) or applied field (electro-magnetic influence) are the primary effects. The temperature idea is well confirmed by the phase transition (at about 42.5ºC) behaviour, and the surprisingly good fitting of Arrhenius-plot to the experimental results.
On the other hand, there are no doubts about the strong heat-dose (energy absorption) dependence, which is shown by the treatment-time relevance in laboratory and clinical results. Also the cell

destruction results support the heat-centred idea: the results are not as good as expected in the case of the systemic heating, where the homogenous temperature could be guaranteed. The loco-regional hyperthermia, which has a little lower and inhomogeneous temperature distribution, looks more successful.
More recently, numerous scientific theories concentrate on the vital significance of the thermally induced but basically non-thermal effects. They back up their view by the thermally and non-thermally generated chaperone proteins, which are most of the case heat-shock proteins (HSP). Chaperones (stress- or heat-shock-proteins) are highly conserved proteins, which are vital in almost every living cells and on their surfaces during their whole lifetime, regardless their stage in the evolution. Intensive research shown those proteins, modify the stress tolerance their action in the programmed cell death (apoptosis). Any kind of change the dynamic equilibrium of the cell life (environmental stresses, various pathogen processes, diseases, etc.) activate their synthesis. Excretion of the chaperones is the 'stress-answer' of the cells to accommodate themselves to the new challenges. As a consequence of the stressful 'life' of malignant cells, the molecular chaperones are present in all the cancerous cells to adapt the actual stress to help tumor-cell survival. Moreover the shock-proteins are induced by every oncological treatment-methods, which are devoted to eliminate the malignancy: after conventional hyperthermia, after chemotherapy, after radiotherapy or even after photo-therapy was shown the intensive HSP synthesis. On the way of the stress adaptation the induction or over-expression of the stress proteins generally provide effective protection of the cell against apoptosis. Furthermore, induction of various HSPs (HSP27, HSP70, HSP90) was observed in numerous metastases and the HSP90 homologue, GRP94 may act as a mediator of metastasis generation. HSP generally degrades the effect of the hyperthermia therapy because it may increase the tumor cell survival, and its massive induction may generate the tumor thermo-tolerance and in parallel drug- and radio-tolerance. Heat treatment can also lead to a multi-drug resistance.
Non-thermal effects (mainly field stresses) could also produce chaperone-synthesis. The HSP manifestation in the biopsies could give a good clinical indication for the treatment response.
On the other hand, the chaperone HSP70 assists to freeze the actual dynamic equilibrium (the "status-quo") and so try to reestablish the cellular communication in the extra-cellular electrolyte. It is shown that their expression on the cell-membrane gains the apoptotic signals and enhances the immune reactions. HSP participates in the activation of the p53 tumor-suppresser and has been associated with the tumor-suppresser retinoblastoma protein.
Stress-proteins have an important role in immunology, having two apparently opposite actions:

1. their induction in the cell interior elongates the cell survival, the malignant cell with their assistance can be more resistant against apoptosis, anticancer drugs, immune attacks or even for hyperthermia, as well as may their massive presence increases the metastatic potential;
2. however, due to their helper capability in the extracellular matrix (ECM) HSP could defeat the cancer-process, (helping reestablish the cell communications) even could be the basic of the anti-tumor vaccination as well.

The anyway high heat shock protein concentration of tumor cells increased by the applied heat. The HSP-assisted adaptation mechanism degrades the efficacy of thermo-treatment and may generate a heat-, multi-drug- and radiation-resistance. Additional result is the HSP generating effect of magnetic field, which basically has to be avoided.
However, there are only a few studies about the field-effects in hyperthermia. Nevertheless, in connection with the applied electromagnetic effects various technical questions arise: how to choose the various frequencies, which applicators and couplings could be the most effective for the energy transfer. The applied electromagnetic field in hyperthermia can affect the chaperones (stress-proteins) expression and therefore it may have an intensive impact on the immune response of the tissue. Considering the mainly completing application of the hyperthermia to classical oncological methods, the potentiality of the parallel chemo- or radiotherapy as well as pre- and postoperative synergy is also influenced by electromagnetic fields.
OncoThermia (electro-hyperthermia) is devoted to enhance the efficiency of conventional hyperthermia by additional, -mainly thermally induced,- non-thermal effects with the aim of suppressing the existing disadvantages of the classical thermal treatments. The absorbed energy from the electric field effectively heats up the extra-cellular matrix (ECM), because the electric-coupled

energy is primarily absorbed in the ECM as it is not able to penetrate through the membrane of high field strength (more than 1 million V/m) (Fig.1). Therefore the directly heated area will be ECM. (Fig.2.)

Fig.1. The electric "encapsulation" of a cell:

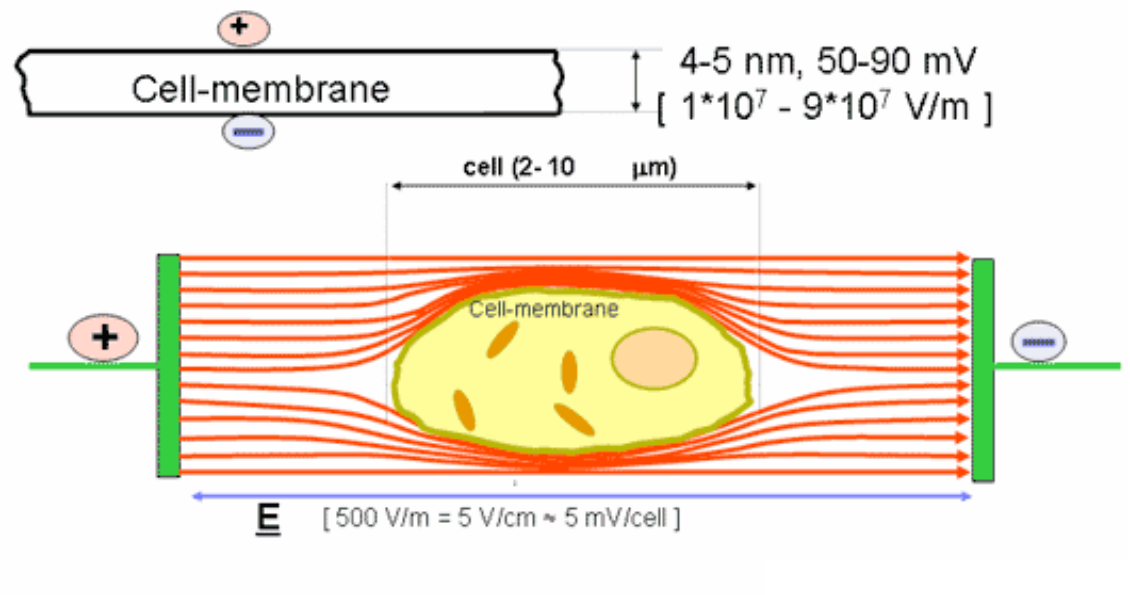
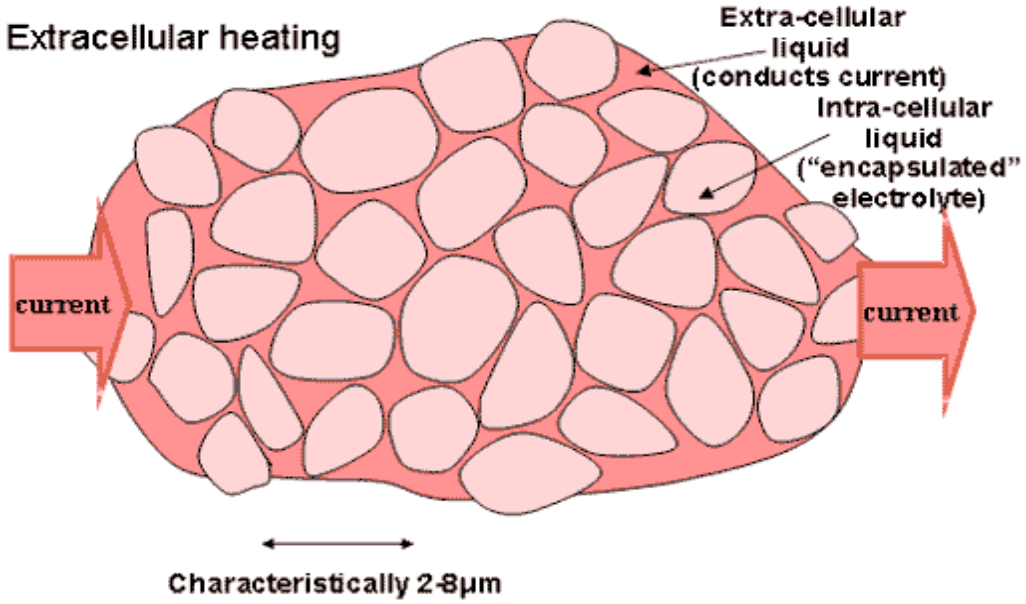


Fig.2. The RF-current flows through the extra cellular liquid:



The dominant extra-cellular action is the main advantage of the well-tuned (personalized and automatically matched) electro-hyperthermia. The cytoplasm of cell will be heated by heat diffusion through the membrane alone. The heat (from the absorbed energy) penetrates only into the cell by diffusion, which acts considerably slower in the cell than the direct heat does in the extra-cellular liquid. Moreover, the suppressed primary intracellular field absorption reduces the non-thermal HSP synthesis.
The temperature in the relatively small volume of extra-cellular electrolyte increases rapidly. Simple and approximate calculation can be done considering the volume ratio of the inter- and intra-cellular

material from the measured average temperature of the treated mass. The speedy temperature rise at the membrane surface can rapidly reach the critical 43o C temperature to damage the membrane. Accompanying the absorbed energy induced heat-effects in the extra-cellular matrix, the applied radio-frequency electric field stresses the highly polarized cell-membrane (from the extra-cellular side), and injures it in the same way as the heat does without prompt stress-protein synthesis in the cell interior. The energy absorption at the applied frequency is proportional to the tissue conductivity and the square root of the dielectric constant of the targeted material. The conductivity in malignant tissue is about three times higher than that of normal tissue. Furthermore, the dielectric constant of the extracellular matrix at the applied frequency is also higher in the malignant tissue than in the healthy one. Change of the dielectric constant is even higher than the measurable value. Measurement indicates only the average of the dielectric constants in the measured volume as this tissue volume is far from homogeneous. Non-homogeneity and disorder characterize the malignant growth observed by NMR measurements and supported by theoretical considerations. As a consequence of the bond-disorder in extra-cellular liquid, a high dielectric constant is to be expected at the applied frequency. As higher electric conductivity is accompanied by higher dielectric constant, the extra-cellular matrix in the malignant regions absorbs more energy than in healthy areas. In well-matched electro-hyperthermia the above selective absorption works like a self-focusing mechanism. Further focusing effect can be derived from the coherent electric waves, with spontaneous breakdown of the polarization symmetries.
Thermo-statically the membrane damage by heat is not effective. Even the opposite: the membrane potential itself changes by the temperature with slope -0.22 mV/K. The temperature equalization for the cell is also very quick, about 10 ms, not allowing long-time existing instability.
However, a tremendous heat-flow, 1500 nW/mm2, permanently transmits through the membrane. It is well above the natural heat-flow by metabolism, which is only 20 nW/mm2. Moreover, the temperature gradient (contrary to the quick equalization) is extremely high: 1 K/mm. The great heat-gradient in the cell allows (by the Onsager relations in non-equilibrium thermodynamics) distinct membrane currents because of its definite thermodynamic driving force. The forced current is also remarkable high: 150 pA/mm2, which is dominantly Na+ influx into the cell. These currents, however, do not conform with the natural ion currents (which is 12 pA/mm2, sodium efflux) and so their presence strongly decreases the dynamic stability of cell membrane.
In addition the thermal flux induces high pressure increase in the cell, reaching 1.32 MPa. The mutant cells have an enhanced concentration of phospholipids in their membranes, making it rigid. Consequently the actual pressure has a selective action to destroy the malignant cells.
Helping effect to destroy the malignant cell, that the diode-like behavior of the membrane absorbs increased energy from the RF current. This effect raises more the membrane temperature, which helps to gain he diode-absorption higher. This positive feedback gains further the membrane temperature.
These processes allow a very important effect: the cell membrane of malignant cells is damaged before the heat reaches the cell-nuclei to synthesise HSP to adapt the stress of invasion. However, membrane HSP is induced by the extreme heat at the membrane, which are supporting the apoptotic signals, to eliminate the malignant cells on the natural way.
Moreover, the elevated temperature distributes tumor-specific antigens on the surface of various tumor cells, and assists in their secretion in the extra-cellular fluid. The extra-cellular HSP90-a has a stimulatory effect on the growth of some lymphoid cells. Chaperones are involved in the antigen presentation in the ECM, and that mechanism increases the immune efficiency.
OncoThermia concentrates on the resolution of these problems by keeping in mind the importance of its known advantages as well. This target may be achieved by utilising two basic effects:

1. As far as possible, this method applies solely electric field not penetrating directly into the cytoplasm. This can be achieved by the application of largely lower field strength than that of the cell membrane potential. Additional feature is the applied special modulation. In this way the energy will be primarily absorbed in the extra-cellular matrix, and penetrate into the cell by thermal diffusion through the cell membrane resulting in the damage of membrane. Consequently, the HSP synthesis starts too late to exert its retroaction and because of the locking out of field there is not any extra HSP generation. As the HSP can be regarded as a very important component in the adaptation process this effect will decrease the chance of adaptation itself.

2. The applied frequency is able to the selective heating. Mainly the tumor cells and tissues without collective connections are heated. This effect is based on the one hand on the differences between the dielectric constant and dielectric loss, on the other hand on the selective absorption features of bound water.

Interactions with other treatment modalities

1. The advantage of combining hyperthermia/oncothermia with the classical ionising-radiation is unambiguous. Principally, the heat effects the anyhow hypoxic tissues automatically as opposed to the ionising-radiation effecting on the tissues with good oxygen supply. If there is a patient having well-founded contra-indication for the actually required radiation-dose, the same result may be obtained by use of smaller radiation dose combined with hyperthermia. So, the hyperthermia/oncothermia well completes the ionising radiation.

Effect/Method	**Ionising radiation acts**	**Hyperthermia acts**
action of cell division	in M+G_1-Phase	in S-Phase
pH-dependence	in alkaline tissues	in acidic regions
Oxygenation	in well oxygenated	in hypoxic tissue

Table 2: Completing of radio-effects by hyperthermia

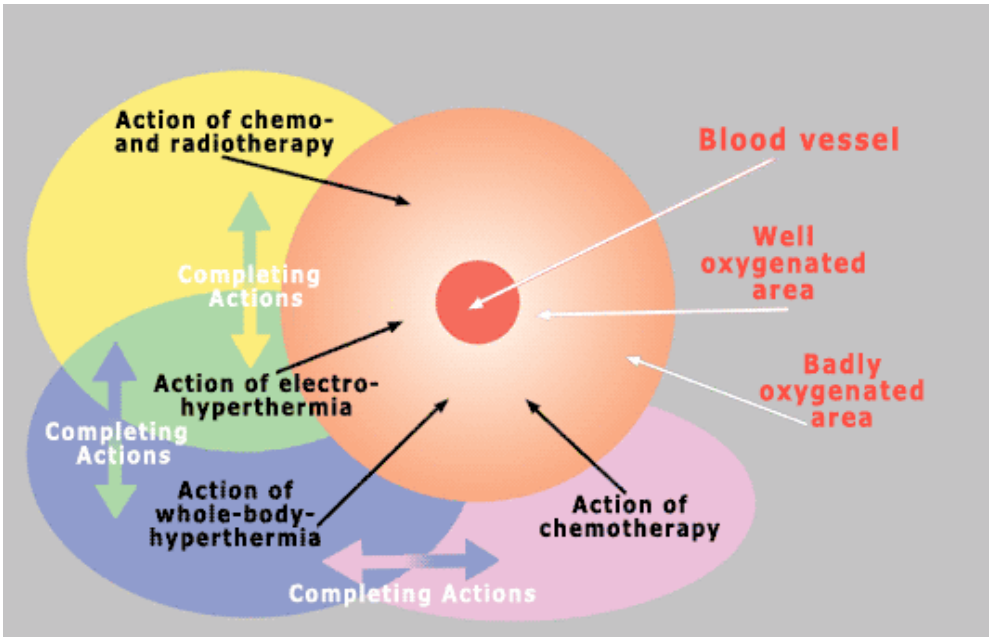
2. The applied drugs delivered into the tumor tissues through the blood circulation. Therefore the effect of chemotherapy is more reactive beside the arteries. In this respect the same area is affected by chemo-treatment as in the case of ionising radiation. Consequently the chemotherapies (systemic, regional or local) can be complemented by hyperthermia. Moreover, a robust synergy prefers the combination of chemotherapy with hyperthermia: the thermally increased metabolism means enhanced reaction rate of drugs, increased absorption of cytotoxines. In case, when the patient is not allowed to take big doses of drugs (for example at renal or liver insufficiency) the same results may be achieved by the combination of decreased chemo-dose and hyperthermia.

Effects/Method	**Chemo-therapy**	**Hyperthermia**
Cell division	Acts in M+G_2 Phase	acts in S-Phase
Chemo penetration	Low, due to high pressure	gained by electro osmosis
Chemo metabolism	Weak	good
Place of activity	At arteries	far from arteries
Reaction rate	Low	enhanced
Activity	No in G_0-Phase	kicks out the G_0-Phase cells

Table 2: Completing of chemo-effects by hyperthermia

3. Completing of the hyperthermia methods with classical oncological modalities is also effective in the very inhomogenous and complex topology of the tumor. (Figure). Magnifying a blood-vessel in the tumor, its vicinity is relatively well oxygenated compare to the tissues more far from the vessel wall. Both the radio- and chemo-therapies mainly act in the vessel neighbourhood, because of their higher activity in oxygen-rich tissues and the blood-delivered drug diffusion, respectively. The electro-hyperthermia targets the relatively hypoxic tissues, with a distance from the blood vessels, so the compliting in the targeted tissue areas is also effective. Furthermore, the systemic hyperthermia completes the loco-regional electro-hyperthermia, because the systemically heated

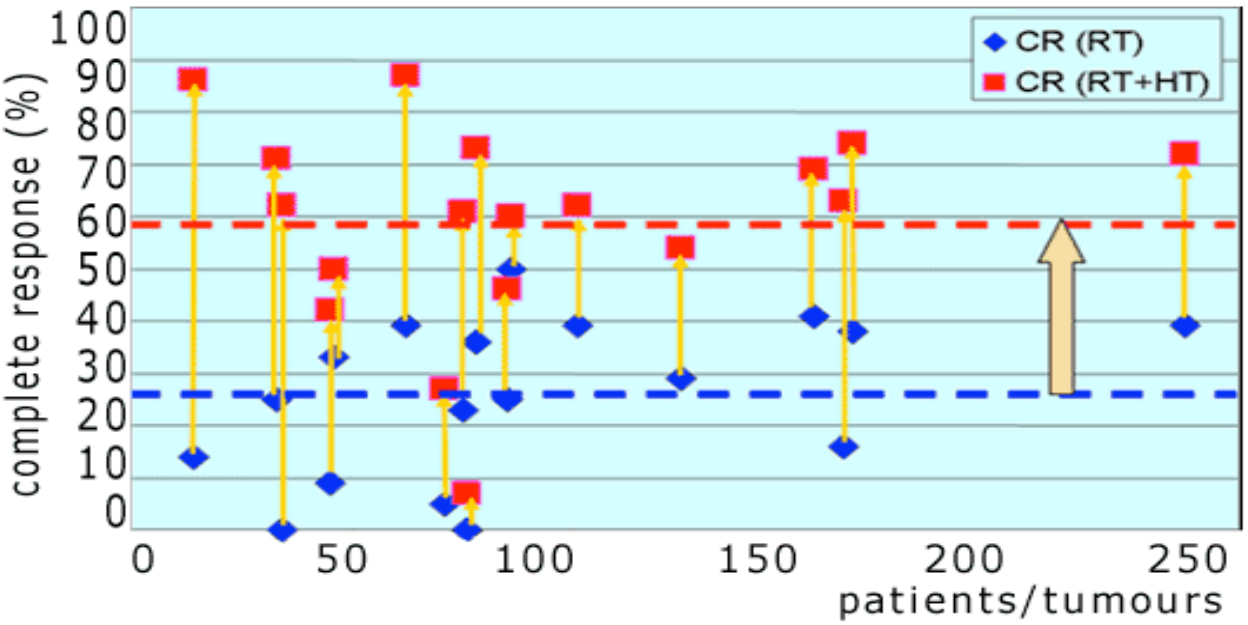
blood primarily targets the vessels neighbourhood (Figure). With the development of the electro-hyperthermia devices we were able to achieve that the hyperthermia could be one of the new, safe and reproducible modalities in oncological treatments with an expectable serious success. By the application of electro-hyperthermia we believe that a new era has started in hyperthermia, and this method can be one of the successful oncological treatment methods in the near future.



Completing of the methods

Complete response on radiotherapy with and without hyperthermia

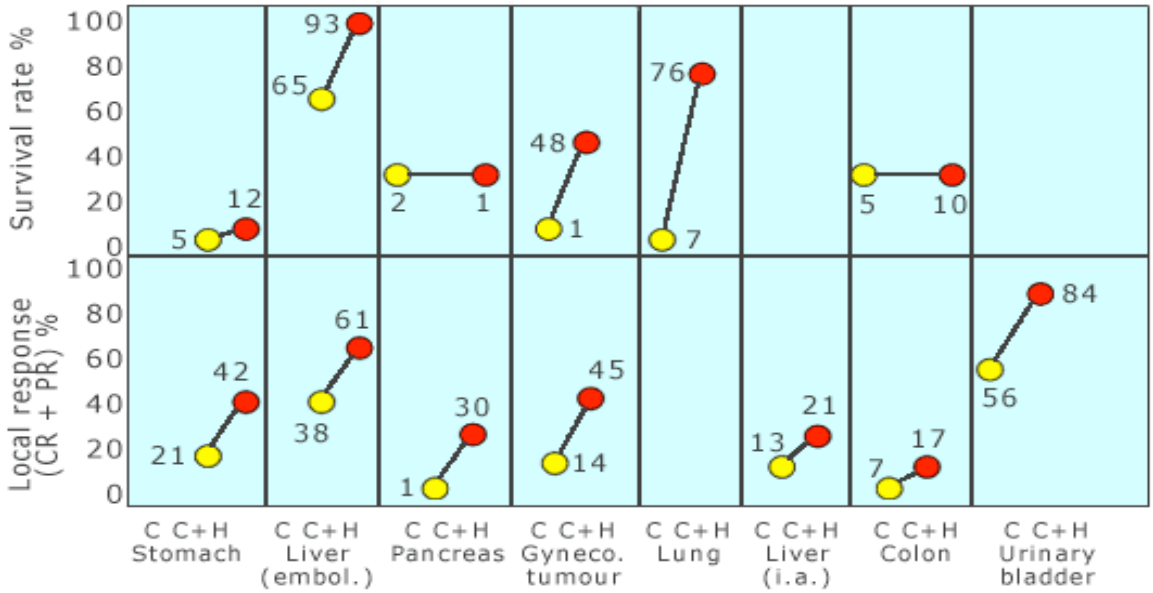
(results of 18 clinical studies, averages: RT:25.6%, RT+HT:59.2%)



(From: J. Overgaard: The design of clinical trials in hyperthermic oncology)

Success-rate of hyperthermia with chemo-therapy:

(Statistics based on 22 clinical articles, including 862 cases)



Treatment:

- C: Chemotherapy alone (specific. [mostly: Adriamycin, Bleomycin, Cisplatin, Mitomycin C, 5FU]), immediate before or during H
- C+H: Chemotherapy plus hyperthermia (hyperthermia: 40-60', 8MHz, 42 C, 4-16 sessions)

(From: T.Sugahara, I.Yamamoto: Clinical response of hyperthermia …
Biomedical Engineering, Application, Basis, Communication, 6, 340-362, 1994

OncoThermia Clinical results

Hyperthermia research is connected to the mainstream of the well established evidence-based medicine, developed and inspected by the Universities and Research Institutes.
OncoThermia cancer treatment is developed by strict scientific basis, including remarkable massive scientific work of:

- Semmelweis University (Budapest, Ungarn)
- Strathclyde University (Glasgow, Großbritannien)
- Szent Istvan University (Godollo, Ungarn)
- National Cancer Institute (Budapest, Ungarn)
- Fachklinik Hornheide für Tumoren und Wiederherstellung an Gesicht und Haut an der Westfälischen Wilhelms-Universität zu Münster
- Universität Witten/Herdecke (Witten, Deutschland), Lehrstuhl für Radiologie und MikroTherapie Humboldt-Universität zu Berlin (Germany)