Oncothermia summary
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History
Hyperthermia is the oldest oncology treatment in medicine [1]. Contrary of this it is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the selection (focusing) of the heat-effect. These challenges are based on bio-physical and engineering problems. This was the reason why the oncotherm development was made by biophysical origins. Oncothermia is a further development of the traditional, more than two thousand years old [2] oncological hyperthermia method. It solves such technical problems, which were blocking the stable applications. The idea of oncothermia solves the selective deep action on nearly cellular resolution [3]. The main idea is connected to the electric field effect of cancer, worked out by the Karolinska Institute, Sweden [4]. The effect of electric field is a hot topic in science, [5], [6], [7], [8], [9], used in other treatment modalities also [10]. Oncotherm company was one of the firsts who constructed treatment unit, and shown it to the medical community, [11]. The results were amazing, [12]. However, the method was invasive, and the request of the non-invasive safe method was the market demand. This was the start of the oncothermia development in early 1990s. From that time the method was rapidly developing and clearly proven [13]. Note, the electric field effect is widely applied on lower frequencies also [14], [15]. Recently the field became very active [16]. and a clinical trials of other field methods are also in progress [17], [18].

Change of paradigm
Oncothermia is based on the paradigm of the energy-dose control, replacing the single temperature concept [19]. The traditional hyperthermia is controlled the only single thermodynamic intensive parameter, with the temperature. However, the requested job is to kill the malignant cells, for what a definite energy dose is necessary [20]. The historical energy-dose-like control (temperature multiplied by its application time), is physically incorrect, and operates with an overall energy average in the area, instead of a directed and well measurable energy-dose (measured in kJ).

Problematic points in conventional hyperthermia:

- make the focus artificially has many problems, because the malignant tumors have no real boundary (only the benign tumors have boundary). So the focus never could be proper,
- the problem is even more complex to see the technical complications of the focusing in depth of the human body, avoid the hot-spots, and eliminate the natural and necessary movements (e.g. breathing or other) of the patients, as well as avoid the overheating of the surfaces, when the energy penetrates in to the body.
- there are many theoretical problems of the heat-effects in the tumor and healthy tissues, the interactions with the general physiology (including the HSP the hypoxia, etc.).

Oncotherm approach:
1. Apply such mechanism, which is self-selective, (the focusing in this case would be automatic);
2. Make such internal energy-distribution, which is not doing an average heating only, but definitively works at the places where the energy could be applied on the most optimal way.
The first point is approached by the general mechanism of the malignancy: the malignant cells have autonomy (renegades as Weinberg says), they are in permanent competition with the others for the nutrition and for the life-conditions. The healthy cells are generally collective, their control is made by “social signals”, no real competition is introduced only a labor division is active. This means, that the active ionic exchange near the malignant cells (in most of the cases) is more intensive than in their healthy counterpart. This allows the introduced current to find the optimal path, which goes through the best conduction way. So the current goes self-selectively to the malignant cells [21]. Technically (in simple speaking) this is nothing else, only to introduce current through the tissue, ant that will find the malignant cells automatically. We had experiments in co-cultures, and observed the effect in work.

The second point is more sophisticated. Apply energy somewhere could increase the temperature of the target but could do some other works also. Naturally, the absorbed energy increases the temperature. It is, like in the case of ionizing radiation, only a normal “side effect” not that is the desired effect. The expected work is to damage the DNA, to destroy the chemical bonds and rearrange the structure. That is trivial, if the temperature is high enough, could do this rearrangement alone, but of course than everything has this average energy. (If we have a fatty dish after the dinner, we could was it our by very hot water only, but a clever housewife has detergent to reduce the water temperature, and make the job where it must be done - at the surface of the dish, and not waste energy to the non-important volumes.) To make the temperature arising alone in the tissue, could be a problem of the safety and again comes back the selection task. So we have to give the energy not equivalently into the target but specifically to the place where we want do the distortion (like the ionizing radiation does). What is the target? It could not be the cellular interior (nuclei and DNA) because that by non-ionizing radiation needs again high temperature, and the initial problem is not solved. The target is the cellular membrane! If we keep the current in the extracellular matrix than the energy heats up only this electrolyte, and a heat-flow starts from the extra- to intra-cellular regions through the membrane. This heat-flow accompanied by different ionic flows and water transport, changes the Hodgkin-Huxley equilibrium, the membrane became more transparent, and at the end destroyed [22]. (Anyway the transparent membrane also could be helpful to kill the malignant cells, because large concentration of the intracellular HSP could be expressed extracellulary, which has direct effect on the apoptosis and the stimulation of the systemic immune reactions.)

So these points are realized, and called this procedure electro-hyperthermia or oncothermia [23]. Of course many theoretical considerations were done to make this idea working. The membrane effects by the outside electromagnetic field are shown against the old theories [24], [25], [26]. Also the modern fluctuation analysis (fractal-physiology, [27],[28],[29],) supports the oncothermia [30], [31]; as well as the resonance phenomenon is studied and used in the light of a new theory [32]. The hypoxia study [33] and special vector-potential theory [34] helps to complete the method. We also study the possible side-effects of the scattered radiation, [35], reduce the risk, and make the method as safe as possible. The acceptance of the new paradigm is a clear demand of the theory and the practice as well [36].

**Technical solution**

The presently applied radiative hyperthermia devices, operating one order of magnitudes higher frequency than oncothermia, are in fact also capacitive-coupled, because the applicators are definitely in the near-filed arrangements. However, these are far not optimally coupled and their frequency is also too high to be able to provide the desired effects. In oncothermia no artificial focusing needed for selectivity, and no isotherms in space and time has to be controlled. Both effects are solved in oncothermia with a directed electric field. It is a well designed capacitive coupling on 13.56 MHz free-frequency, [37]. Oncothermia is controlled by the changes of the impedance, and by the absorbed energy, which both are accurately measured. In this meaning oncothermia is very similar to the RF-ablation hyperthermia, where the temperature is not measured, the effects is controlled by the measured impedance of the tissue. The power is ranging form 30 W to 150 W, which is far enough for
heating up the tumor over 42 ºC in a well controlled focusing. (You may touch a working 12 W halogen lamp to be sure on its burning efficacy. Less than 20 W is enough to heat up a 5 cm diameter tumor from 36 ºC to 44 ºC at 3 minutes! The only clue is the focusing.)

Oncothermia requests technically two definite effects: selectivity and cell-killing. [38],

**Selectivity** – Oncothermia is selective by the higher conductivity and higher permittivity of the extracellular matrix of malignant tissue. (This high complex dielectric constant is effective in the microscopic level as well.) The higher ionic concentration in the more active cellular environments and different physiological conditions (see PET, [positron tomography]), allows even spatial resolution by this effect (EIT [electric impedance tomography] and CDI [current density image]). Oncothermia is selective by the higher conductivity and higher permittivity of the extracellular matrix of malignant tissue [39]. The high complex dielectric constant is effective in the microscopic level as well. In coculture experiments the healthy fibroblast remain intact, while the aggressively malignant melanoma cells (A431 cell line) are destroyed (Fig. 1) [40].

**Fig.1. Selectivity in vitro experiments: only the aggressively malignant A431 cells are destroyed in a coculture with non-malignant fibroblasts (Dr. Brunner, Münster)**

The selectivity is well demonstrated on the brain treatment of mice, where the sharp selective focusing on cancer area is also shown, Fig. 2. The in vivo experiments well support the in vitro results. The excellent focusing of oncothermia can be proved by the temperature measurement in the tumor and the surrounding healthy muscle (Fig. 3.).

**Fig.2. Selectivity in vivo experiments, (fixed sample): The definite borderline of the GL261 murine glioma (brain) tumor in nude-mice shows the tissue selectivity**

Two kinds of treatments were performed: local classical hyperthermia and oncothermia (Fig. 4.) Both of the treatments were controlled by accurately measured intratumoral temperature with fluoro-optical method.
Fig. 3. Selectivity in vivo experiments: A) HepG2 tumor xenografted nude mice with temperature measurement probes in the tumors: . B) comparative energy-absorption (temperature) measurement

Fig. 4. Experimental setups of hyperthermia and oncothermia

The method to calculate the killing rate of the treatments is a morphological comparison based on the observed pathological differences. The living part being in intensive proliferation microscopically could be easily distinguished from the necrotic part containing the dead tumor cells. We compared the area-change of the dead part of the control and treated tumor originated from the same animal. The differences are significant, (Fig. 5.).

Fig. 5. The macro-evaluation of the efficacy of oncothermia in comparison to the hyperthermia in HT29 tumor xenograft. Change of the areas of dead and vivid parts in percentage of the untreated control on the same experimental animal (data average of 3 animals each). Similar experiments were carried out with the same results for A431 human epidermoid carcinoma xenograft model and GL261 murine glioblastoma model

Comparison of hyperthermia and oncothermia combined both methods with mitomycin-c (MMC) single dose chemotherapy in vivo at tissue and cellular level using histological examinations is shown on Fig. 6. HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mouse. 2 animals for hyperthermia (42°C) + 3mg/kg MMC ip. (30min before the treatment); and 2 animals for oncothermia (42°C) + 3mg/kg MMC ip. (30min before the treatment).
The cell-killing effect of the method (%)

A) Hyperthermia 42°C + MMC

B) Oncothermia 42°C + MMC

Fig. 6. Investigating the difference of the effects of i.p. administered Mitomycin CA) The cellkilling is relative to the control tumor on the same animal. (Two-two animals was measured with double tumors on each for control.) B) Hemalaun-eosin stained microscopic images of tumor samples.

The temperature dependence was also investigated [41]. The same temperature application of the two thermal treatments was tried together with the only field application (cooled back) case (Fig. 7.). It was clearly shown the advantage of oncothermia where the electric field has significantly higher effect as the temperature; as well as they have good synergy in cell-killing process (Fig. 8.) [42].

Fig. 7. Comparison of cell-killing effect of hyperthermia and oncothermia at different temperatures.

Fig. 8. A sample of the temperature pattern of hyperthermia and oncothermia at different temperatures.

Oncothermia is based on the modulated electric field effect, which works in synergy of the classical temperature-based hyperthermia concept. In preclinical conditions (in vivo and in vitro) many measurements were done in animals and there are many interested users who tried up till now the temperature development by the method, which is a complex, invasive measurement approach. The latest, sophisticated, well-controlled clinical temperature measurement was done in Nurnberg (Klinikum Nord) by Prof. Dr. H. Renner. The CT-guided fluoroptic sensor was positioned by
interventional radiologist, and the patient (suffering with advanced sarcoma) was treated with the medium applicator. The result is shown on the figure. The maximal temperature in the tumor was 44 °C, while the surface temperature remained around 32 °C.

**Lethal cell-disruption** – The constrained thermodynamic transport effects destabilizes the cell-membrane, increases its permeability and could make its bobbling and distortion [43], [44]. These are high efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart, Fig. 9. It also produces higher concentration of HSPs in the outer membrane and in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis.

![Fig. 9. Lethality comparison with traditional hyperthermia in vitro experiments (fixed sample): HL-60 leukaemia cell line](image)

The setup made possible a fine temperature control, which allowed to keep the heating, keeping and cooling dynamist also identical, Fig. 10. This makes identical heat-shock protein induction by the temperature changes. The temperature dependent equality was controlled by luciferase transient transfected HEK293 cell lines [45].
Fig. 10. The dynamism of the heating and cooling is also well controlled for comparison of the two heating methods.

Fig. 11. HSP70 distribution in A431 epithelial cancer cell-line xenografted nude mice tumor samples treated by hyperthermia and oncothermia (Immuno-fluorescence microscopic images, red:HSP70, blue: cell nuclei)

Despite of the equal temperature curves, oncothermia produces higher concentration of HSPs in the outer membrane and in the extracellular matrix (Fig. 11.) The higher HSP concentration, in the vicinity of the malignant cells is one of the factors to induce apoptosis.

Change of adherent connections (E-cadherin and β-catenin) are also indicators of the gain of the social signals promoting the apoptosis [46], [47]. Remarkable change could be observed on beta-catenin dynamic development by time after the treatment, Fig. 12. on HepG2 human hepatocellular carcinoma cell-line. This considerable change after 24 hours of the treatment is sharply different from hyperthermia on the same temperature, and supports the other observations of the non-temperature dependent processes [48]. The sudden regrouping the beta-catenin and its enrichment at the cell-nuclei could be an indicator of apoptosis [49].

Fig. 12. Development of β-catenin by time elapsed after the treatment in comparison of untreated and hyperthermia as well as oncothermia treated samples. Sampling: 1h, 3h, 24h after the treatment; (Immuno-fluorescent microscopic images, red: β-catenin, blue: cell nuclei)
Detecting the double strains of DNA (DAPI staining, Fig. 13.) and measuring the enzymatic labeled strain-breaks of DNA (TUNEL-FIIC, Fig. 14.) the apoptosis is highly likely in oncothermia, while at identical temperature in classical hyperthermia the necrosis is preferred. Consequently the main effect in oncothermia is the apoptosis contrary to the conventional hyperthermia, which operates mainly by necrosis.

**Fig.13. DAPI staining (stains the double strains of DNA only)**

**Fig.14. TUNEL-FITC staining (enzymatic label of the strain-break of the DNA)**

Many in vitro and in vivo preclinical studies as well as twenty years entirely positive practice and huge number of retrospective clinical studies are behind of oncothermia.

Remarkable amount of retrospective clinical studies are available to indicate the oncothermia effect in humans [50]. It is commonly used for such a complex and very frequent tumors like lung, liver, pancreas, brain, gastrointestinal, gynecological, etc. Prospective evidence based clinical trial was not performed till now with oncothermia. The reasons are:

1. it is applied over the second line of treatments (far advancer cases). No evidence based trials exists in this treatment line for pharmaceutical products also.

2. The evidence based studies are too expensive compared to the facilities of the company.

3. Most of the users run a private clinic, having no interest to make such studies.

Retrospective studies and case reports on huge number of patients show amazingly good results in all the registered localizations. The best enhancements are in the brain-gliomas (n=, %). The retrospective analyses in independent clinics show coherence in the success, and definitely and significantly higher survival time than the large databases (SEER [51], Eurocare [52]).

The oncothermia challenge is its small fraction only of the overall survival. Oncothermia is applied when other treatments fall, consequently the patients with long overall survival could have not observable life-elongation, even if oncothermia was effective. The aggressive disease with short survival is a chance to indicate the efficacy. For these reasons we compare the 1st year survivals rate
only (see fig 15.). In this sense oncothermia is indicated as a feasible, effective method [53]; [54], [55], [56].

<table>
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<tr>
<th>#</th>
<th>Localization</th>
<th>Patient number</th>
<th>SEER 1st year survival (%)</th>
<th>Eurocare 1st year survival (%)</th>
<th>Oncothermia 1st year survival (%)</th>
<th>Oncothermia 2nd year survival (%)</th>
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<td>1</td>
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<td>80.63</td>
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<td>15</td>
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<tr>
<td>4</td>
<td>Ovary</td>
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<td>27</td>
<td>223</td>
<td>16</td>
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<tr>
<td>5</td>
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<td>257</td>
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<td>9141</td>
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<td>43082</td>
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Fig. 15. Comparison of the first-year survival rates of various cancers with the large databases. Improvement of the first-year survival percentages of oncothermia (advanced patients) compare to SEER and Eurocare data weighted average.

On brain-gliomas, the Groenemeyer Institute (Bochum Germany) was active [57], [58], [59], [60], [61], [62], [63], together with the BioMed Clinic (Bad Bergzabern, Germany), [64] [65]. [66], [67], [68]; as well as the Empoli University had publication, [69]. Presently two German Universities (Regensburg [Prof. Bogdahn] and Heidelberg [Prof. Wick] are working on prospective clinical study on brain gliomas with hyperthermia. A dose escalating Phase I clinical study was made on Neurology Clinic, University of Regensburg, showing the safe process in the brain as well, [70]. The safe treatment could be shown by spectacularly documented near-eye cases, when the tumor disappeared by the oncothermia treatment, while the eye remained unhurt, intact from the treatment [71]. To see more evidences we show the retrospective data of independent clinics [72], having the same oncothermia protocol (Fig. 16.). The data are well correspond to each other and significantly higher than the data of the large international databases.

Fig. 16. The median survival and the first year survival in comparison with different clics, having the same oncothermia treatment protocol.

The metastatic liver tumor is a very complicated issue due to the effective cooling of the large blood flow and the sensitivity of the organ due to the chemo-toxicity from previous treatments. Our results are also exceptionally good for that organ. The colorectal liver metastasis was the topic of four different studies on liver [73], [74], [75], [76]. The sensitivity of the liver on the chemotherapy in advanced cases (when the other chemo-treatments were unsuccessful) is well observable on the combined treatment compared to the oncothermia monotherapy, Fig. 17. [73].
The pancreas carcinoma is a rapid and aggressive disease, and not too many conventional hyperthermia results can be found in this location, [77]. Oncothermia results presented on ASCO, [78], and other conferences [79], [80] are significantly improving the achievements of the conventional treatments. Results were repeated in six different clinics in two countries (Fig. 18), and so the gain definitely made on statistical evidences.

The lung is also a complicated organ for hyperthermia because of the permanent cooling-ventilation of the breathing. Oncothermia, due to the non-equilibrium approach, is an excellent treatment for that as well, [81], [82], [83], Fig. 19.
Also remarkable effects were published on bone tumors [84], [85] using oncothermia.

**Legal note**

According to European Medical Device Directive (MDD) oncothermia is certified by TUV, Munich. All the devices are manufactured according to the ISO9001 and ISO 13458. Safety and efficacy are certified also by TÜV Product Service München. The device works over 100 places actively, and the oncothermia is twenty years on the market. No serious toxicity or side effects were reported. Minor adipose burns were happen in about 3% of all the large number of treatments. Anecdotal benefit: patients report less side effects from the conventional treatment if oncothermia is complementary applied. They report furthermore better quality of life and improved well-being.

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