WHAT IS RELEVANT IN HYPERTERMIA TREATMENT:

HEAT, TEMPERATURE, FIELD OR SOMETHING ELSE?

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ABSTRACT

There are intensive discussions in the scientific communities on the quality-parameters of hyperthermia. Most of the parties are convinced that only the temperature decides about the optimal treatment, but strong doubts are also exists declaring the delivered heat (absorbed energy) or applied field (electro-magnetic influence) as primary effects. Strong points of the temperature-supporters are the results of all the investigations which are concentrating on the temperature-dependence and the effectivity of Arrhenius analysis showing a phase transition at about 42.5 C, (this is the basic of the step-down heating). On the other hand no doubts about the strong heat-dose dependence, which is most trivial by the treatment-time relevance in the clinical and laboratory results. The field effects in the hyperthermia does not investigated so widely, but trivial questions arise to choose the techniques, different applicators, frequencies and couplings.

We had developed a set of the hyperthermia treatments applying various mixes of the heat and field effects. Four methods are applied successfully, where the heat- and field-effects are involved by different ratio for various malignant cases. Among the four methods there are a method with only electric field application (ECT, percutane, no heat), moderate heat with moderate field (PCT, cavitational), dominate local heat and electric field (EHY, loco-regional) and almost no field, only heat (WBH, whole-body application). The reached temperature in the tissue does not determined only by the absorbed heat, physically other effects have decisional role in the measured temperature. The applied power in the various methods is very different, ranging from a few watts to the few kW, while the electric field ranges from a few tens [mV/cell] to the few [nV/cell]. Due to the large and essential inhomogenities of the well-developed tumors only the average temperature could be defined in most of the cases. Same average temperature is reachable by different applied power, only depending on the power-delivery conditions. This observation strongly supports the importance of the heat (energy) absorption [W/kg] in the tumor instead of the only temperature conception.

Results show the excellence of the optimizing the method to the actual case. With all the four treatment modalities we have surprisingly good results by choosing the most optimal for the given case and combining the applied methods with each other. Results by the different electro-hyperthermia applications will be shown in the presentation. The loco-regional applications are massively applied in deep-organ treatments (pancreas, liver, brain, etc.), while the cavitational is devoted for prostate, bladder and gynecological, etc. cases. The percutane local treatment is very effective for mammary-carcinomas, for head- and neck-cases, malignant melanomas, etc. The IR-A radiative whole-body hyperthermia is very useful in metastasizes, in systematic cases, etc.

According to the intensive laboratory and clinical experiences and strong evidences we can conclude, that beside the temperature the heat-delivery as well as the field effects are primary important for the oncological hyperthermia.
The electro-hyperthermia effect is based on different physical principles and scientific results, (Fig.1.). The classical hyperthermia was based only on the heat (for example they used hot-bath (water or wax) or other surface heaters (heat-blanket). This effect was mainly to change the pH-environment of the malignant tissue by the elevated temperature, based on the higher rate of metabolism. In the last decades the development of the hyperthermia was directed in two ways:

1. Deliver the heat into the requested area targeting only the tumor.
2. Use other effects (for example: electric field to modify the cell-membrane channel-permeability, which is a voltage-gated effect).
3. The parameters are interconnected., (Fig. 1.).

Electro-hyperthermia uses high-frequency well-tuned electric field to self-focus the energy absorption. The energy absorption in these frequencies is proportional with the square root of the dielectric constant of the material. The dielectric constant is much higher in the malignant tissue than in the healthy one, so the energy absorption is also different. The general difference could be pretty high ($\varepsilon_{\text{healthy}} = 1-50$, $\varepsilon_{\text{malignant}} = 80-90$), so the self-focusing is technically possible, (Fig.2.).

The machine specially constructed with capacitively coupled applicators (the patient is the dielectrics in a condenser) and carefully tuned to have the best SWR. The machine does it automatically and measures all the electric parameters to keep controlled the procedure. The forwarded and reflected power and the phase shift (complex impedance) are measured. For the temperature calculation the measured absorbed energy and the impedance is used.

The hyperthermia is an oncological modality by the heat-treatment. The heat-treatment for the non-specialists always connected only with the temperature. For specialists the temperature is only one of the relevant parameters (a very important one), but other thermodynamical parameters are also crucial.

The well-cooled applicators take possible to avoid the surface burning and take...
Because of the good selectivity and addressed heat absorption, during these conditions no hot spots could be created, because the heat-energy is not enough for the heating up such a relatively large mass as the treated one to the 45 °C. The tuning of the antenna is based on the electro-dynamic antenna calculations.

The dielectric conditions in imperfect dielectrics, in which \( \epsilon \neq 0 \) and \( \frac{\sigma}{\epsilon_0 c} \ll 1 \), and we know, that \( \left( \frac{\epsilon}{\epsilon_0}, \mu = \mu_0 \right) \). The attenuation factor is: \( \alpha = \frac{\sigma}{2 \pi c} \left( 1 - \frac{\sigma^2}{8 \pi^2 c^2} \right) \). And the propagation factor: \( \gamma = \frac{\sigma}{2 V_c} \left( 1 - \frac{\sigma^2}{8 \pi^2 c^2} \right) + j \mu_0 \frac{\omega}{c} \left( 1 + \frac{\sigma^2}{8 \pi^2 c^2} \right) \). While the phase velocity and the wavelength:

\[
\frac{\omega}{\beta} = \left( 1 - \frac{\sigma^2}{8 \pi^2 c^2} \right) \quad \text{and} \quad \lambda = \frac{2 \pi}{\beta} \left( 1 - \frac{\sigma^2}{8 \pi^2 c^2} \right) + j \frac{\sigma}{2 \omega c} \]  

The intrinsic impedance, \( Z = \frac{\mu_0}{V_c} \left( 1 - \frac{3 \sigma^2}{8 \pi^2 c^2} \right) + \frac{\sigma}{2 \omega c} \), is based on the electrodynamic antenna calculations.

The heat-effectivity of microwave cooking in this meaning is similar to the oncological hyperthermia, where we have to measure first of all the absorbed energy. Because the heat-treatment target is not the whole body, but its regional area, it is even more important, that to monitor the energy-absorption in the targeted area. The pumping procedure of the heat into the depth of the body has some physiological limitations, Fig.4.

Only an average temperature could be defined, for what this specific energy is optimal. The temperature calculation characterise the tissue temperature in average, but the extracellular liquid in this average has much higher temperature (due to the dielectric constant differences) than the intracellular one, Fig.5.

One has to know that the temperature has huge gradients inside of the malignant tissue. The malignant area is not homogenous the blood perfusion is very different in the region. A typical arrangement is shown in the attached picture, copied from the special issue dealing with cancer of the Scientific American. This shows the good blood perfusion in the periphery, which stabilises the surface temperature of the tumor. This is like a heat shield for the outside heating procedure. That is the reason, why the RF electric heating has so large importance: it heats in-situ inside the tumor, the energy is absorbed inside the heat shield, Fig.6.

On the other hand the tumor-mass is also very complex, having a special structure of the normal and hypoxia parts. This inhomogeneity affects on the energy-absorption and so on the temperature-distribution as well, Fig.7. We have to be careful to detect the temperature.

That is the point why the touching temperature measurements are not useful (and not applicable in RF field). Only an average temperature could be defined, for what this specific energy is optimal. The temperature calculation characterises the tissue...
temperature in average, but the extracellular liquid in this average has much higher temperature (due to the dielectric constant differences) than the intracellular one. This is a point of the huge effectivity of the method, because the high temperature in the extracellular matrix pushes the chemical equilibrium in lower pH and extraordinary increases the outside ion-mobility, which gains the metabolism to overload the cell. (All the ATP is combusted, the cell is empty energetically, starts the anaerobe, fermentative oxidation.)

The invasive temperature measurement has also problems of inhomogeneity. If we measure outside the tumor-mass, than the measurements is false, because of the surface heat shield of the defected mass. The outside heat on the other hand is also a consequence of false energy absorption, the delivery not concentrated enough on the malignant tissue. It means the temperature inside could be much different, and even not characteristic. The change of the blood-flow during the heating-up procedure as well as the pressure change parallel to the treatment are also factors to change the temperature in the area. The energy-dose (if it is directed to the targeted area) the best characterization of the treatment effectivity. The dose after a huge averaging and penetrating on the heat shield appears on the body-surface as well, Fig.8.

That is the point why the touching temperature measurements are not useful (and not applicable in RF field).

The other effect is connected with the electric field and its modulation, mainly acting to the Ca-ion influx and Na-ion efflux. This is a huge helping effect.

The aim of the cancer treatment is to stop the malignus processes and destroy the existing tumour. The critical target of the damage is the cell membrane.. The well-known advantages of the hyperthermia based on the pure heat effect, with the main problem how to deliver it into the proper place. The heat effects are of course important, but in our present paper we would like to focus mainly on the problems connected with the basic conception before, and which are not considered often in hyperthermia applications. (The tumor structure is complicated fractal structure as shown in Fig.9.)

The local hyperthermia has some well established and widely spreaded methods to deliver the most optimal heat for treatment. Among these is one of the oldest the capacitive-coupled RF-hyperthermia, which is applied in many Clinics. We put this method into the focus, because it has such advantages which are not available in the other kind of hyperthermia-treatments.

The capacitive coupling applies a special capacitor for antenna, in which the patient is the dielectric. The heat delivered by the energy-loss of the material,
As we had discussed the characteristic signal-isolation process for malignancy caused by the disordered states in water based electrolyte. The disordered aqueous solution at the same time has higher real ($\varepsilon'$) and imaginary part ($\varepsilon''$) of the dielectric constant $\varepsilon = \varepsilon' + j \varepsilon''$, $[j = \sqrt{-1}]$. The real part [$\varepsilon'$, polarisability] is enhanced by the disorder itself, while the imaginary [$\varepsilon''$, loss] part is gained by the higher ionic mobility in the disordered electrolyte. Both parts are frequency and field-strength dependent. This means, we can optimise the energy-absorption by the applied frequency and field. The dispersion and loss spectra of the disordered and well ordered (ice) water shows characteristic difference by the ordering: the ordered water structure has a high constant ($\varepsilon' \approx 95$) in small frequencies $[< 1 \text{ KHz}]$, while it is small ($\varepsilon' \approx 5$) in higher $[> 10 \text{ KHz}]$. The sharp decrease of the $\varepsilon'$ in disordered case is considerable shifted to 10 GHz. Furthermore the dielectric loss also characteristically differs in the two cases: the ordered water has a loss peak with maximum at about 7 KHz, the maximum for the disordered one is at about 80 GHz. On this basis the best frequency would be in the RF $[1 \div 100 \text{ MHz}]$ interval. Supports this choose that the aqueous protein solution (disordered state) has a plateau between 0.8 - 1000 MHz with about $\varepsilon' \approx 75$.

The extracellular disorder in malignus tissue means that the electric field absorption is self-focused on to the tumour’s intercellular electrolyte. The electric field energy delivered most effectively to the intercellular liquid of the malignus area, which really gives the best, most effective membrane distortion by heat-effects. During the treatment the thin intercellular layers will be warmer than the detected average tissue temperature, in which the actual main heat-absorbent is only a small fraction. The dissociation constants are temperature dependent. Due to the relatively high temperature, the pH of both the intra-- and extra-cellular liquids decreases; so acidic poisoning becomes effective. Moreover, the effect is even better, because of the pH decrease is different in between the internal and external liquids. In consequence of acidic environment of the malignus cell tends to more acidic by the temperature, which can be a factor of the selective treatment as well. The forced decreased of the pH due to the massive acidic poisoning stops the stimulating chemical loop.
The other advantage of the electro-hyperthermia is that by the well-applied electro-magnetic field (well-chosen voltage and frequency modulation) can stop the stimulating depolarisation currents, abolish the positive feedback physical loop. This effect is manly based on the electric field, forcing a transport of ions in the intercellular region, where the disordered water allows higher conductivity.

The other electromagnetic field effect is associated by the voltage-gated and ion-gated channels of glycosylated membrane proteins which are responsible for the signal-transmission of cells. There are (not regarding the special proton-pumps) three important ion-channels in the membrane: sodium-, potassium- and calcium-ion channels. Channels can be controlled by a few mV, and only pA currents are involved in the conduction. The growth of the cell is associated with the development of the ionic currents flowing through the cell. These initialise a non-equilibrium polarity of the cell, with that instability is introduced to signalise the division. The calcium ion transport seems to be an essential current to predict cell instability to divide. A special modulation frequency can essentially modify the Ca$^{+}$-flux. The external electric field applied by the electro-hyperthermia modulated by the appropriate frequencies can effect to these processes, and so this could be a contributing effect to the electro-hyperthermia action.

We are using for this all the advanced results of so called ‘fractal physiology’. We are convinced (as it established in fractal physiology) if all the dynamical bioprocesses follow the harmonic (pink) noise than the absorption of these special self-organised noises supports the normal bio-functions. This is the reason, why to apply such noise-signal-modulation to help the healing procedures. It has to be mentioned, that to stop the chemical and physical loops an invasive electric field treatment (galvano-, electrochemical-) is also applied widely.

Of course not only the capacitively coupled RF-heating affects the above listed and studied malignant processes, but all the electric field applications can be good candidate for treatment. We have applied electric field by invasive electrodes (galvano-methods) obtaining success on the same manner.

### What are the differences?

<table>
<thead>
<tr>
<th>level</th>
<th>cell</th>
<th>tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>healthy</td>
<td>$\beta$ - stage</td>
<td>$\varepsilon \approx 3 \div 25$ (order)</td>
</tr>
<tr>
<td></td>
<td>$V_{\text{membrane}} = 60 \div 75$ mV</td>
<td>controlled ion-transport</td>
</tr>
<tr>
<td>malignant</td>
<td>$\alpha$ - stage</td>
<td>$\varepsilon \approx 80 \div 90$ (disorder)</td>
</tr>
<tr>
<td></td>
<td>$V_{\text{membrane}} = -20 \div 40$ mV</td>
<td>non-controlled ion-transport</td>
</tr>
</tbody>
</table>

### Electromagnetic “answer” of the tissues (morphological differences are neglected)

<table>
<thead>
<tr>
<th>Frequency range</th>
<th>Tissue type</th>
<th>Healthy tissue</th>
<th>Malignant tissue</th>
<th>OUR METHOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC (0 Hz)</td>
<td>low DC conduct.</td>
<td>high DC conduct.</td>
<td>ECT</td>
<td></td>
</tr>
<tr>
<td>LF - RF (0.1 - 10 MHz)</td>
<td>high AC impedance</td>
<td>low AC impedance</td>
<td>ICT</td>
<td></td>
</tr>
<tr>
<td>HF - RF (10 - 100 MHz)</td>
<td>low diel. constant</td>
<td>high diel. constant</td>
<td>EHY</td>
<td></td>
</tr>
<tr>
<td>MICROWAVE (3-30 cm, 1-10 GHz)</td>
<td>H$_2$O absorb.</td>
<td>H$_2$O absorb.</td>
<td>NOT applied</td>
<td></td>
</tr>
<tr>
<td>INFRA-RED (A) (0.8 - 1.4 $\mu$m)</td>
<td>“water-window”</td>
<td>“water-window”</td>
<td>WBH</td>
<td></td>
</tr>
<tr>
<td>VISIBLE (0.4 - 0.7 $\mu$m)</td>
<td>Colorfull</td>
<td>Less colorfull</td>
<td>Surgery</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

We have studied three remarkable characteristics of the malignant tissue:

1. disorder of the intercellular electrolyte,
2. decreased pH and connected chemical loop,
3. depolarisation current and connected physical loop.

These phenomena give possibility to affect on malignus processes by combined the heat with the external electric fields and its special modulation affecting on the potential-gated ion-channels in cell-membrane.

We suggest the special capacitively coupled hyperthermia (electro-hyperthermia) uses not only the heat but the electromagnetic interactions as well to force the actual cell-membrane states out of malignancy. Equipments constructed on this way are working in some of the Clinics.

Self-organising fluctuations are measurable in any parts

The living system could be checked by 1/f noise

Which system specifically emmits, that adsorbs the same as well

The living system could be organised by 1/f noise

Diagnostics

Treatment
LIVING DYNAMISM:
BIFURCATION ON EVERY LEVELS

ENERGY

ENERGY

dynamic equilibrium

individual state

collective state

TRANSLATIONAL

BIFURCATION

DIRECT

INDIRECT

WATER

MEMBRANE

PROTEIN

CELL

TISSUE

ORGAN

ORGANISM

translation

bridge

unsaturated

ordered

stage

‘maser’ state

action state

“Yang”

central

monomer

saturated

disordered

incoherent state

rest state

“Yin”

Structural arrangement

CANTOR DUST

\[
D \approx \frac{\log(2/\log(3))}{\log(3)}
\]
Systematic whole body hyperthermia

WBH - 2000

OncoTherm

PCT 2000

OncoTherm

Cavitational Cancer Treatment

ECT - 2000

Electric Cancer Treatment

Electro-hyperthermia system

PCT

2000

OncoTherm

EHY 2000

Cavitational Cancer Treatment

ECT - 2000

OncoTherm

Electric Cancer Treatment

Electro-hyperthermia system
Uncaging morphology was pancreatic tumor with survival quality of life in the severe allergic asthma and further was moderately angiogenic. The growth of the metastasis was seen.

A 45-year-old doctor with multiple liver metastases at the time of diagnosis was treated with 5-fluorouracil (5-FU) and leucovorin (LV). The number and size of lesions became smaller after 15 sessions. The level of CEA (carcinoembryonic antigen) fell during the treatment.

Addition for Design: direct liver metastasis