WHAT IS RELEVANT IN HYPERTHERMIA 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.

INTRODUCTION – What is the problem?

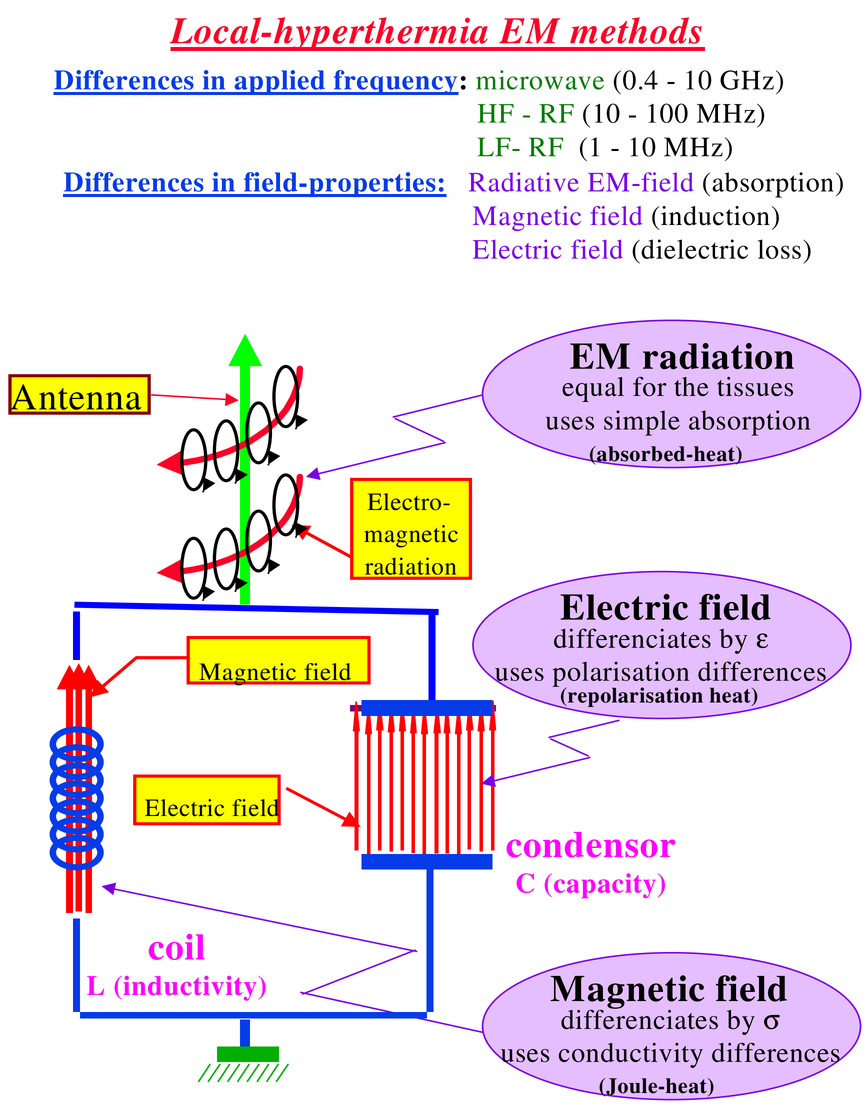

Figure 2. Different electromagnetic effects for treatment

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 ($\varepsilon_{healthy}$ = 1-50, $\varepsilon_{malignant}$ = 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.

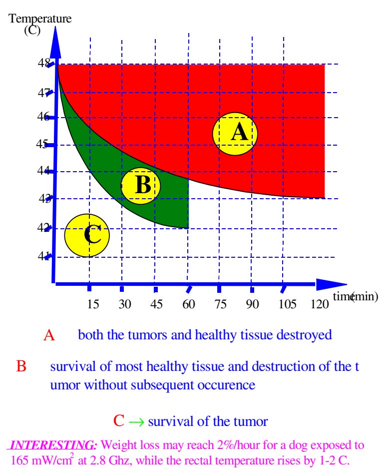

Figure 3. Heat-dose approximation

Let we note a trivial everyday household heat-treatment procedure: the cooking. Make a proper dish in simple cases we use water or grease to stabilise the temperature of the system. The stabilised temperature 100 °C for water-content dishes, 270 °C for grease content dishes, all stabilised by the phase-transition procedure: the water or the grease could not be heated up more than their boiling temperature. If grease and/or water disappear from the system, that would not be stabilised ever more, the temperature becomes uncontrolled, the dish suddenly becomes black-burned. The result of cooking determined mainly by the time of cooking, so the heat-dose (absorbed energy) is important physically. The oven-cooking situation is more similar to the medical hyperthermia, the applied temperature become more important, the self-regulation of the treated system is not counted. That is why the temperature of the oven becomes important parameter of the cooking. Also the heat dose (temperature and cooking-time together) determines the success. In the microwave cooking the temperature of the oven is not relevant, because the absorbed energy is not temperature dependent. Only the absorbed energy is measured by an attached timetable for the actual microwave cooking. The recipes describe the procedure by the knowledge of the microwave power (low, medium or high) and by the time the heat-dose has been calculated, Fig.3.

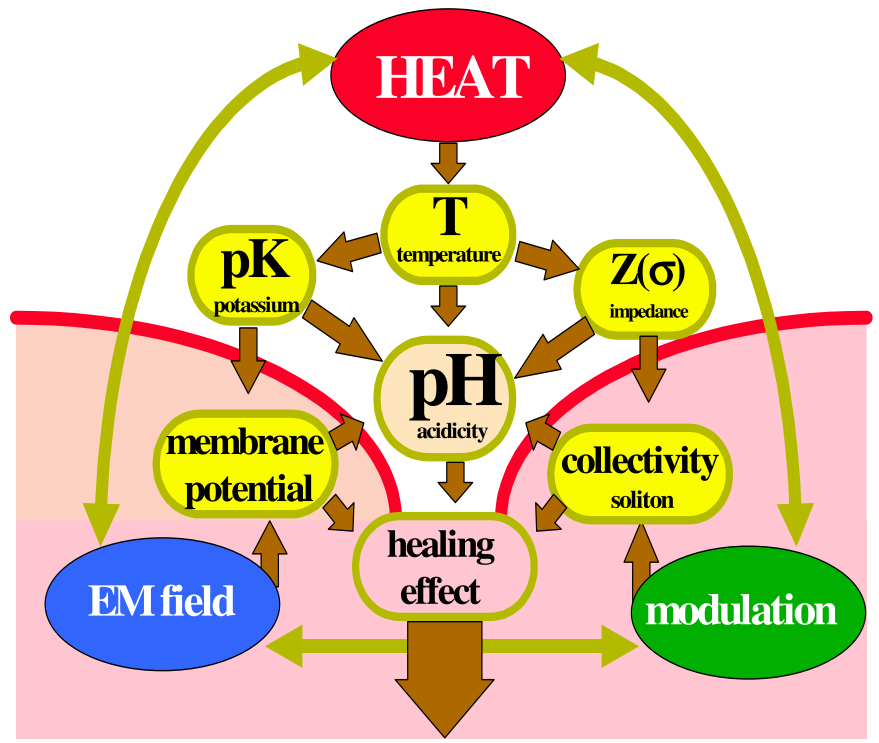

Figure 3. Effective parameters and their interconnections in electro-hyperthermia

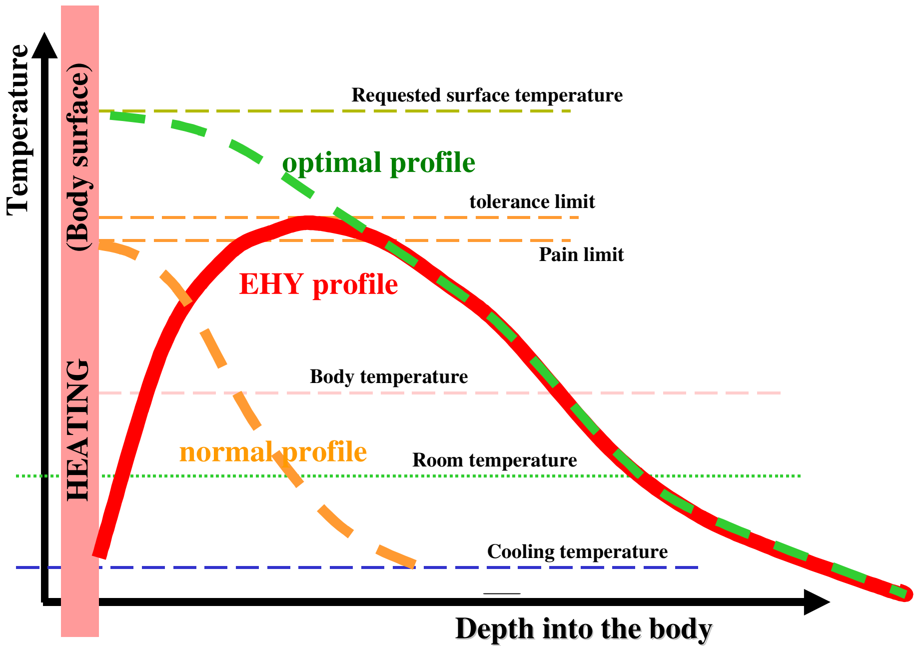

Figure 4. Temperature distribution in depth of the body and some limits.

The well cooled applicators take possible to avoid the surface burning and take possible the higher power without any overheating risk, Fig.4.

Relatively small total power could be applied 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 ^{o}C.

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.

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 calculation is roughly shown in the next chapter.) The pumping procedure of the heat into the depth of the body has some physiological limitations, Fig.4.

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 inhomogenity affects on the energy-absorption and so on the temperature-distribution as well, Fig.7.

To detect the temperature we have to be careful where to measure.

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 characterizes 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 oxidization.)

The invasive temperature measurement has also problems of inhomogenity. 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 not applicable the point why the touching temperature measurements are not useful (and 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.

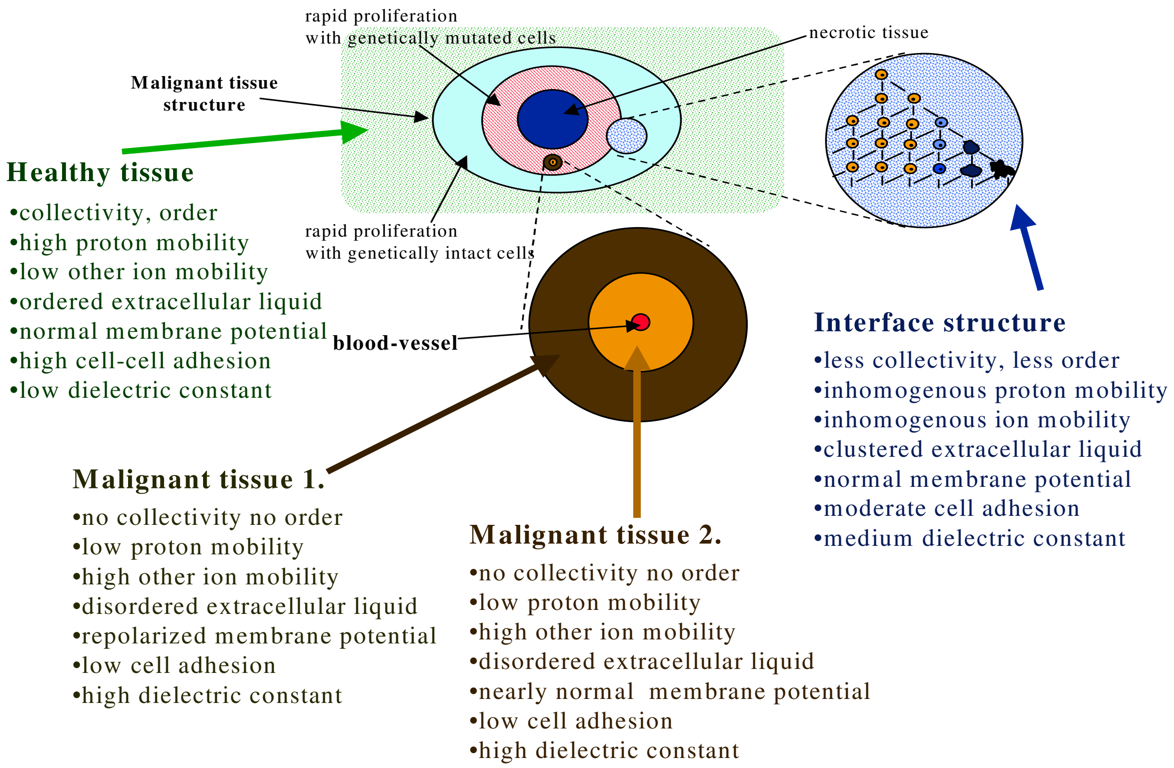

Figure 7. Complicated structure of the malignancy

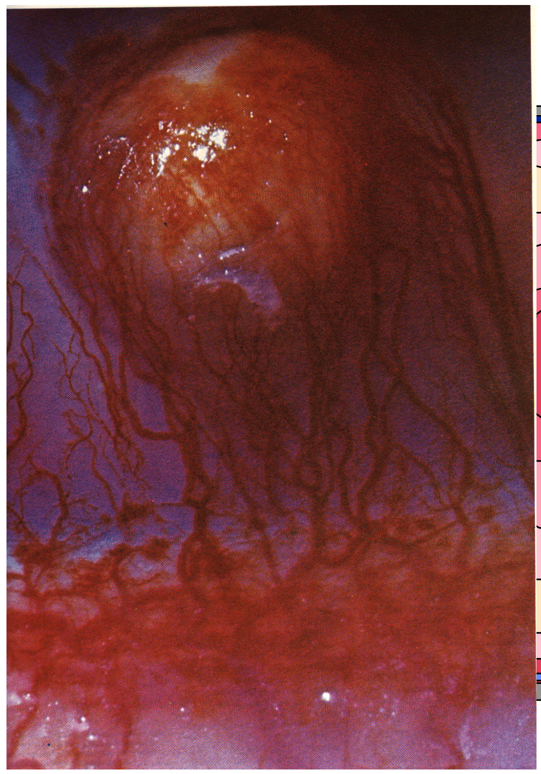

Figure 6. Blood-perfusion on the tumor boundary, works like an effective heat-shield

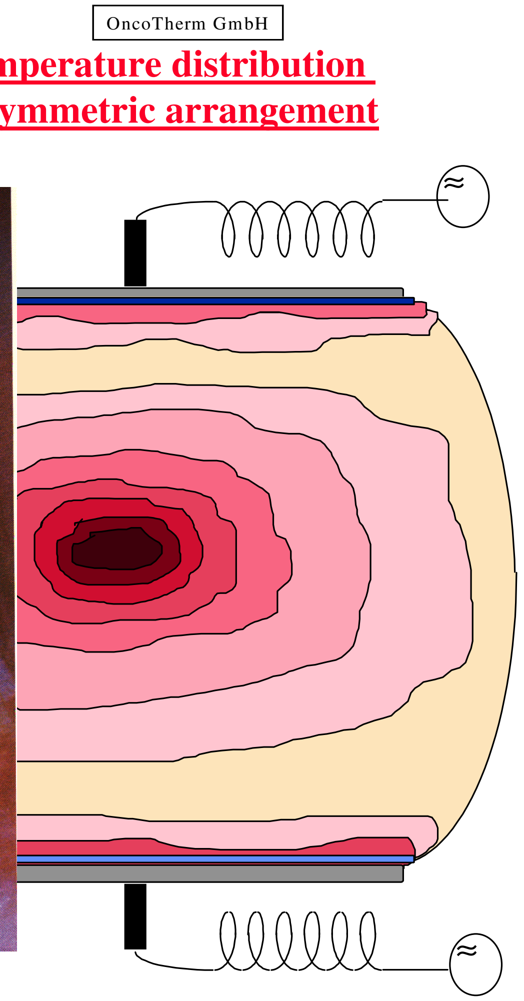

Figure 2. Selectivity draft of the electro-hyperthermia

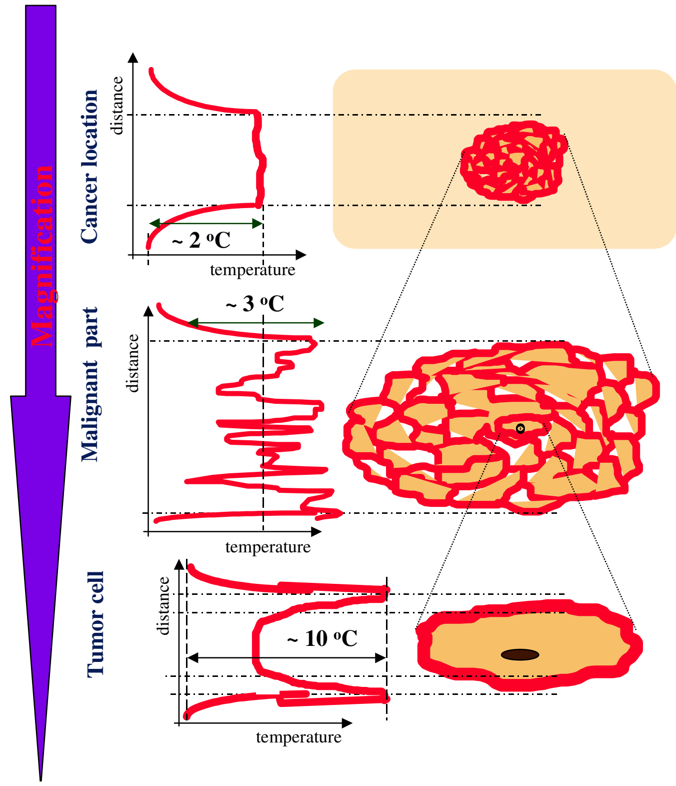

Figure 5. Some temperature gradients caused by electro-hyperthermia shown by magnification in the tissue

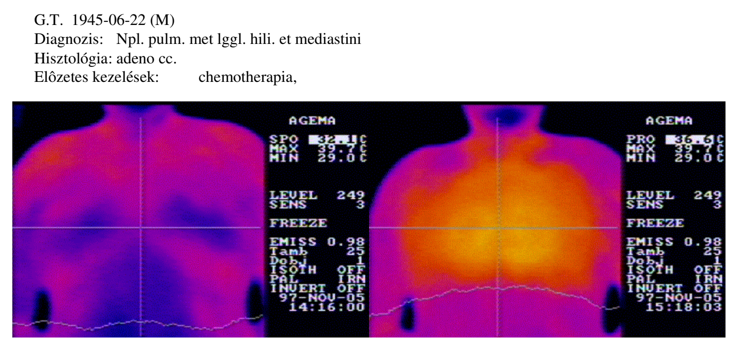

Figure 8. A sample thermo-picture shows the surface temperature before and after the electro-hyperthermia teratment.