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Oncothermia protocol

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Abstract

Oncothermia is a highly personalized treatment modality. It is not a "gold standard" yet, but it is on the way to reach its position as a "fourth column" among the main oncotherapy modalities. It has wide-range applicability for every solid tumors in all possible localizations, irrespective its primary or metastatic form. It could be applied complementary to all the known oncotherapy methods. It is applicable in higher lines of the therapy protocols, even in the refractory and relapsed cases as well. Its applicability contains the curative and palliative approaches as well as it is well personalized to provide the optimal available treatment for the given case.
The main factors to fix a personalized protocol are

(1) the complementary treatment, [decisional basic is the protocol of the "gold standard" therapy],
(2) the tumor entity,
(3) the personal status
(4) physiological factors of the patient.

The most frequently applied bimodal treatments are the oncothermia combined with chemotherapy or radiotherapy. While in trimodality it is combined with the radio-chemo-therapy. The general considerations of the oncothermia application are:

(a) step-up heating to make better HSP differentiations;
(b) Weibull-distribution development of the heating progress;
(c) keeping the physiological adaptation time-intervals;
(d) keeping the blistering safety

Oncothermia protocols are developed for every treatment areas as monotherapy and as in combination with gold standards. The main points of the common consensus are:

a) electrode is chosen according to the target volume, as large diameter as possible on the lesion,
b) step-up heating is used. The heating function is the physiologically adequate Weibull distribution,
c) Weibull parameters (shape/form (approaching) and time/unit (saturating) are determined for various targets,
d) the physiologic reaction time (usually 6 min) is desired for changes,
e) treatment time is 40-90 minutes depending on the lesion, electrode-size and personal sensing,
f) frequency of application depends on the conditions and complementary applications,
g) it is possible to have high number of treatments (chronic palliation method),
h) some sensitive organs have to be slightly loaded by higher doses and by modulation,
i) complementary to radiotherapy needs evaluation of blood-flow (radio-sensitivity)
j) complementary to chemotherapy needs to evaluate supporting the chemo-infiltration and the chemo-metabolism in the tumor.

Our objective is to propose protocols for various treatment conditions, to make a frame which has to be filled up by the actual and well personalized details.

Oncothermia clinical philosophy

Hyperthermia is an ancient treatment. It was the very first one in oncology, but it could not find its established place among the "gold standards" of the oncotherapies. The controversial results were

originated from the paradigm to constrain the temperature growth in the process. The constrained forces made physiological contra-reactions keep the homeostasis, which unfortunately contains the malignant tissue as well. The actions have to be selective, and have to be gentle enough to work together with the natural processes, and not against them.
Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat-flow on the membrane supported by the electric field effects). It is natural, it is not against the homeostasis and physiology does not work against the action. The main task is to direct the physiology in the standard way, and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium have to be stopped.
Oncothermia follows the update demands of the modern oncology:

- It is a personalized therapy,
- It is non- toxic,
- It elongates the survival time of the patients,
- It completes the curative actions with increased quality of life
- It has good cost/benefit ratio

The introduced new paradigm by oncothermia solved the classical challenges:
■ Challenge (1): "The biology is with us while the physics is against us" (Overgard J., [1]).
✓ *Oncothermia solution:* "The biophysics is with us"
■ Challenge (2): "The biology and the physics are with us while the physiology is against us" (Osinsky S., [2])
✓ *Oncothermia solution:* "The fractal physiology is with us"
■ Challenge (3): "Reference point is needed!" (Fatehi D. van der Zee J., et. al. [3]).
✓ *Oncothermia solution:* "Back to the gold standards, use the energy instead of temperature"

Oncothermia is serious in its **3E&3S** concept:
3E
Efficacy of the energy-absorption and dose
Efficacy of the natural selective cell-killing
Efficacy of the survival elongation and quality of life

3S:
Safety for patients with treatments by highest standards
Safety for doctors by low radiation, user-friendly application
Safety for legal and economic points by high-scientific basic

Oncothermia status in the world

Oncothermia is applied in five continent of the world, providing approx. 100.000 treatments yearly. Its distribution by countries is shown on Figure 1.

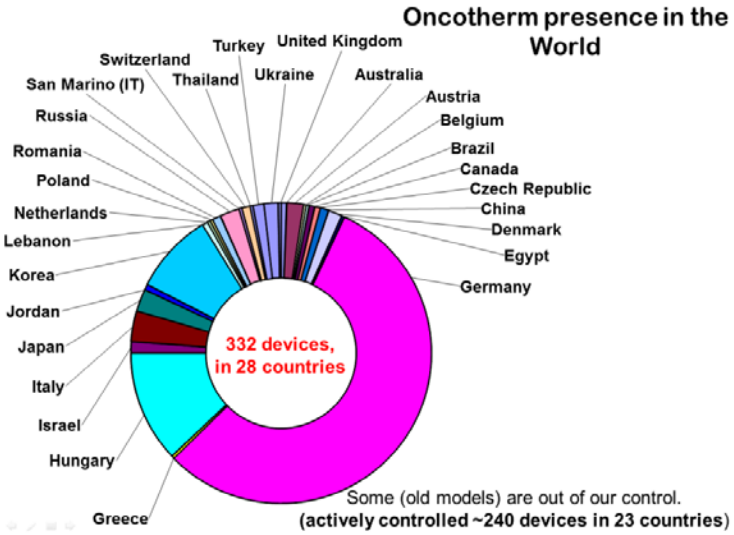


Figure 1. Oncothermia in the world

Oncothermia has a set of special devices for various applications. These are:

- Oncothermia for laboratory use (EHY105 & EHY110)
- Oncothermia for veterinary use (EHY500)
- Oncothermia for intraluminar treatment (EHY1010 & EHY1020),
- Oncothermia for locoregional treatment (EHY2000+ & EHY2010)
- Oncothermia for multilocal treatment (EHY3000).

The energy-ange covered by these devices is 1 W – 700 W depending on the application. No devices uses intensive cooling (energy elimination) on the surface of the skin, only the patented equilibrium is established.

Oncothermia became active servant for the declared war [4] against cancer.

Challenges in hyperthermia

The central task is to find the proper dose in the given application, and optimize the safety and curative limits of the applied dose. The lower limit is of course determined by the minimal effect by heating and the upper limit determined mainly by the safety issues, like it is usual for overdoses. The lower limit of oncothermia dose is indefinite, because in case of normothermia nothing else has action only the complementary treatment alone, which has no danger and has such curative effect as we expect from the gold-standards. For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering to the 0.5 W/cm^2, (60 min basis) the internal hot-spots could hurt the healthy tissue, and in systemic application the physiology anyway limits at 42 °C. The ultimate challenge is the developing heat resistance, which could make the hyperthermia ineffective, the disease became refractory for heating. The presently applied dose concept (CEM) in conventional hyperthermia is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in extreme case reaches the 42 °C (even the 43 °C is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start make vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40 °C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and

permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.
Hyperthermia overheats the actual target. It does not limit the target size at large (like whole-body hyperthermia) or at small (like heating with nano-particles) volumes. These methods are all characterized by the temperature, but they are characteristically different by their thermal state. In whole-body heating the thermal equilibrium drives the process, the body-temperature characterizes the treatment technically. However the body temperature characterizes the process less and less by decreasing the volume of the heated target, the body temperature becomes stable and almost independent from the local heating of a smaller volume in the body. Contrary to the thermal equilibrium in whole body heating, the non-equilibrium dominates in local treatments, and consequently thermal gradients will appear in the system. Heating in nanoscopic range creates huge fluctuations of the local temperatures while the hot nanoparticles try to equalize their high temperature with their neighborhood. This process is typical for the commercial microwave heating, where not the extra nanoparticles, but especially the water-molecules are heated in their nanoscopic sizes, and those give the temperature to the entire volume by time.
Constructing a nano-heating process the targeting of the nanostructures is a clue. Their selection from the other materials makes their controlled heating and also targeting the heat on the desired volume possible. Extra nanoparticles could be selectively absorbing the electromagnetic energy extremely heating up these small particles in their neighboring spheres. Our approach is definitely similar, but by not using extra particles for selective energy absorptions. Our nanoscopic targets are naturally in the body, in the membrane of the malignant cells. The selection is based on the metabolic differences (Warburg effect), the dielectric differences (Szent-Gyorgyi effect) and beta-dispersion (Schwan effect) as well as uses the structural (pathological) differences (fractal effect) of the malignant lesions.
The main medical advantages of the method are its personalized targeting together with the effective selection and distortion of the malignant cells. The new direction of application focuses on the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. The method is successfully developed in the direction of the immune-support, and a new patent covers an exciting area: cancer-vaccination with oncothermia.

Oncothemia specialties

Avoid from high temperature ("Physics is with us, when we use it well")

- Temperature heats up the vicinity of the tumor, it can not be kept locally focused,
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.),
- Temperature requests the increase of the safety-cooling on the skin,
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely,
- Temperature increases the blood-flow in the region, in consequence increases the dissemination,
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy,
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemopenetration into the tumor (vasocontraction or blood-vessel blockage in the tumor),
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues),
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient.

Temperature is not dose (Temperature is spreading)

- ✓ Moderate temperature avoids the natural contra-regulation effects
- ✓ Temperature does not exceed the systemic physiological limit (42 C)
- ✓ Tumor selection is solved by non-temperature dependent way (electric concept)
- ✓ Focus is to be fixed to the tumor, moves together with the natural body movements (impedance control)
- ✓ Selection is solved on cellular level suppress the dissemination of the malignant cells
- ✓ Cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination
- ✓ Cellular communication (social signal) is reestablished to promote the natural (programmed) cell death for malignant cells
- ✓ Possibility of the cellular molecular exchange (gap junctions) is reestablished to promote the normal function of the cells
- ✓ The "master switch" (p53 gene) is activated promoting the natural way of various cell killing pathways
- ✓ Cell-membrane permeability is increased to express the HSP on the outer membrane signalizing the cell malignancy for the systemic immune actions
- ✓ Cell-membrane is excited to ignite various communication pathways in the cells
- ✓ Electric field blocks the positive feedback loop of tumor-supporting injury currents

Technical specialties of oncothermia (The nano-scale heating)

- Target the cell-membrane in nano-scale (correct energy is mandatory)
- Personalized information-delivery is applied (patented)
- Surface cooling is controlled (patented)
- Low voltage large current (at given energy) is applied (patented)
- Time-fractal modulation is applied (patented)
- No temperature measurement is necessary (patented)
- Every part is designed to the actual task (oncotherm-design)
- Easy to use, comfortable for patient, tailored for patient

Avoid the static approach ("thermostatical considerations are against us")

- Measurement of intensive thermodynamical parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)
- The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept.
- The heat-flow to blood supports the positive feedback loop of the basic-acidic electrolyte balance, and promotes the intensive growth of the tumor by addressed oxygen delivery.
- Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead of its elimination. (These processes like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.)
- Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

Application of dynamic processes ("Thermodynamics and fractal physiology is with us")

- ✓ Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, and does not constrain it for false defense.
- ✓ Control of oncothermia is natural, always fitted to the actual conditions (changes of the electrolytes determines its actions).
- ✓ No considerable heat-flow to the blood-stream by oncothermia, no gain of the positive feedback of electrolyte balancing-loop.
- ✓ Thermal gradients make dynamism in a very local area of the cell-membrane of malignant cells. The applied selection focuses on this thermal non-equilibrium.
- ✓ The relatively slow "step-up" heating keeps the non-equilibrium stable for long time for action.
- ✓ The slow heating up does not create considerable physiological contra-actions.
- ✓ The slow heating makes the healthy tissue adapted to the growing temperature.
- ✓ The slow temperature change does not generate high stress and following stress reactions.
- ✓ The applied electric field makes at least three times more effective cell killing than the temperature does.
- ✓ The applied fractal modulation makes possible the selecting and supporting the natural processes to activate the natural healing mechanisms and reestablish the healthy "social signal' between the isolated cells, promoting the anti-malignancy collectivity.

Avoid automatisms in treatment guidelines (Guidelines are not "cookery books"; we are in the clinic and not in the kitchen)

- Everybody is different….
- The actual disease is not simply the disease of an organ. This organ belongs to somebody.
- The personal differences are modified by the previous treatments and tolerances.
- The definite similarities after the chemo- or other serious therapies are mainly due to the side effects…
- Most of the decisions in serious cases need medical experience, not "only" book-based evidences.
- The patients with advanced diseases are not "naïve" in most of the cases. Their high-line treatments need personal decisions, frequently no evidence-based protocols are available for their special cases.
- Many times the palliation is necessary, which definitely needs personal decisions.
- The psycho-factors are not negligible in the case of malignant diseases.
- The personal decision is the responsibility of the experienced doctor…

Make personalized processes (Guidelines of the thinking for experienced physicians)

- ✓ Oncothermia is mainly regulated by the patient's tolerance.
- ✓ Oncothermia control based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoid burning the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient's natural defending/protective system.
- ✓ Oncothermia uses natural processes to cure, understanding and using these needs thinking doctors and their understandings.
- ✓ Oncothermia acts of natural physiology regulation, which needs understanding of the processes.
- ✓ Oncothermia needs permanent dynamic approach, follow-up well what is happening during the treatment.
- ✓ Step-up heating is the basic treatment approach, which requests permanent care on the process.
- ✓ The effect of the activated natural processes are not acting immediately. To have a control treatment-by-treatment is essential.
- ✓ The patient's well-being during and after the treatment is necessary side of the well conducted protocol.

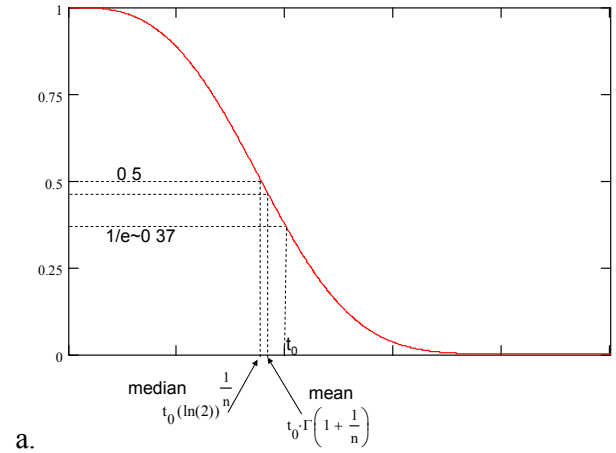
✓ Complete relaxation could be supported by relaxing music, video or sound effects during the treatment.

Physiological basis of oncothermia protocols

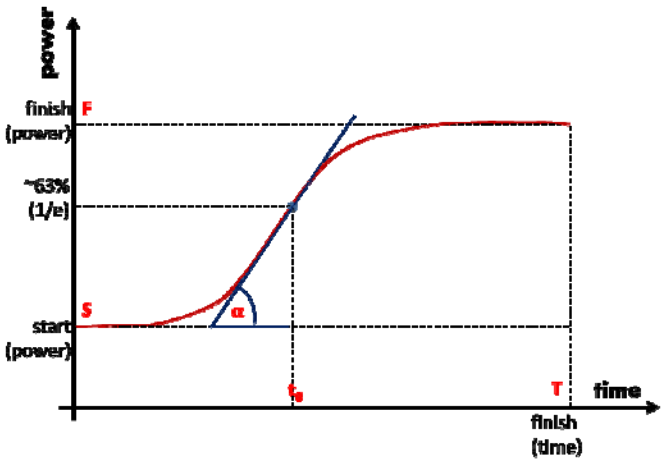
The physiological processes are determined by a dynamic equilibrium process-character, which is dominantly determined by special transports and logistics in the complex bio-systems. The distribution which is typical for general logistics, failure analyses and even for survivals is the Weibull distribution [5], which cumulatively looks

$$f(x) = 1 - e^{-(x/t_0)^a}$$

where t_o is the unit time, when the value of the function is $1/e \approx 0.37$; the a-exponent in the distribution defines the shape (see Figure 2.).



a.



b.

Figure 2. The special points of the Weibull function: the median, the mean and the value, where $t=t_0$ ($1/e \approx 0.37$). The derivative in the inflexion point equal $(n/t_o)\cdot(1/e) \approx 0.37*n$, when $t_o=1$. The popular meaning of the parameters are: t_o is the stretching in x-direction (time-transformation), n is the stretching in y (incline of the curve). This curve (a) shows step-down situation. A growing curve (when it is not deducted from 1) is the step-up situation (b) The parameters which has to be defined are the F, S, T, t_0 and α, the finishing and starting power, the full treatment duration, the 63% of the power-increase and the slope of the power increase, respectively

The a-exponents were observed in various processes in wide range of applications. The generalized logistic function (sigmoid) could be constructed by various ways, but the so called Avrami-exponents (a, which is the exponent of the above Weibull function) are functionally appearing based on the extended works of FW. Cope [6], [7], there are some collected Avrami-exponents for various solid-state (see Table 1.) and biological processes (see Table 2.) show the universality of this logistic function.

Processes in solids [8]	Avrami exponent (a)
Beginning of nucleation	3
Nucleation with constant speed	4
Nucleation with growing speed	<4
Staring nucleation and surface growth	2
Diffusional growth from nuclei	1.5
Diffusional growth from growing nuclei	2.5
Diffusional growth in 1 or 2 dimensions	1
Limited diffusional growth in 1 or 2 dimensions	1.5

Table 1. Avrami exponents of some solid-state processes, [8]

Biological processes [6], [7]	Avrami exponent (a)
Growth of bacteria	4
K^+ conductance decay in nerve axon	1.9
K^+ leakage from poisoned muscle	1.7
Growth (weight) of rat	2.0
Growth (length) of regular leg of salamander	2.3
Growth (height) of sunflower plant	1.9
Synthesis of chlorophyll in maize plant	2.2
Muscle tension during tetanic contraction	1.21
Myosin splitting of ATP	1.24
Fresh green leaf IR photophorescence decay	1.0
Dried green leaf IR photophorescence decay	1.28
Melanin IR photophorescence decay	1.08
Cytochrome c IR photophorescence decay	1.16

Table 2. Avrami exponents of some biological processes, [9], [10]

Application of Weibull distribution function approaching multiple clinical applications and it is well established theoretically and practically, [11], [12], [13], [14]. It is used for a long time for survival description in gerontology [15], [16] and in oncology [17] as well.

Calculation of the median and the mean from the Weibull distribution is a routine [18] by the formulas:

$$median[W(t)] = t_0[\ln(2)]^{\frac{1}{n}} \qquad (1)$$

$$mean[W(t)] = t_0 \int_0^{\infty} e^{-x} x^{\frac{1}{n}} dx = t_0 \Gamma\left(1+\frac{1}{n}\right)$$

However these calculations and definite on the opposite way also: the measured mean and median easily defines an appropriate Weibull distribution, calculated form the parametric formula above.

The ratio of the median and mean depends on only the *n* form-factor. It is rigorously monotonic in the practically interesting range of *n*, Fig. 3. Weibull functions with various parameters are shown on Fig. 4. The function has its inflexion point (where the tendency of decreasing changes) in $t=t_0$ at *1/e* (≈0.37) value, (see Fig. 5.). The derivative in this point is proportional *–n*. (The derivative there is exactly *–n/e* [≈-0.37*n*].) Therefore the parametric evaluation could be well checked in the $t=t_0$ point.

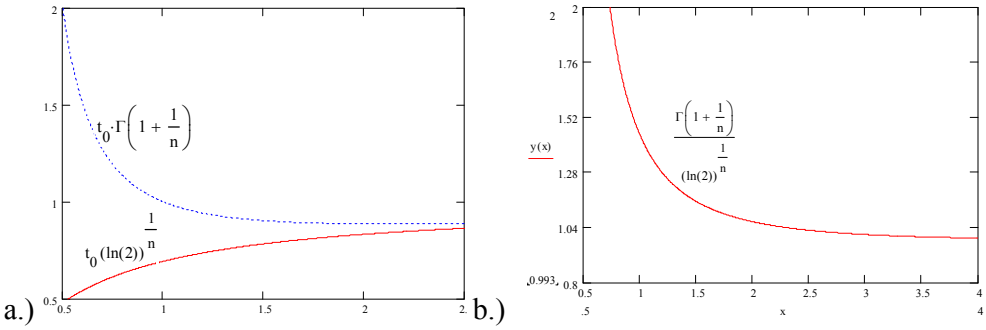


Figure 3. Dependence of mean and median (a) and their ratio (b) by the shape-factor n

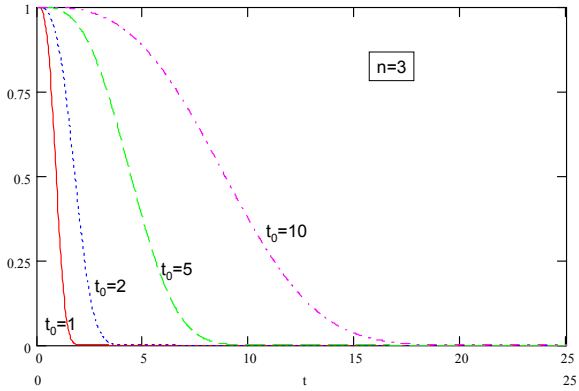


Figure 4. Weibull distribution with various parameters

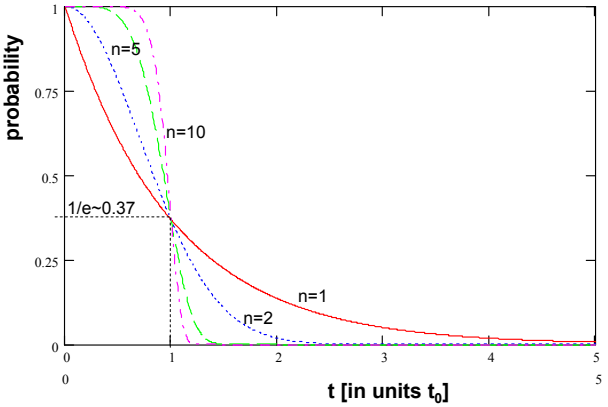
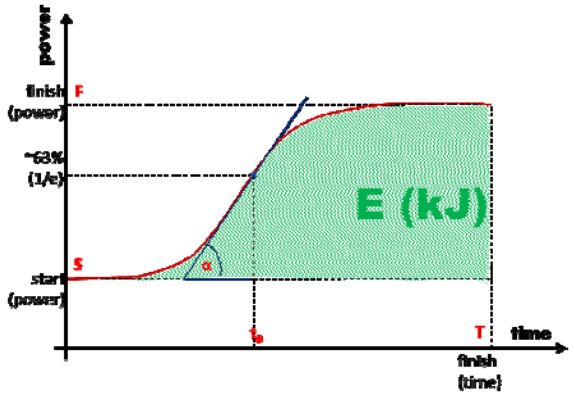


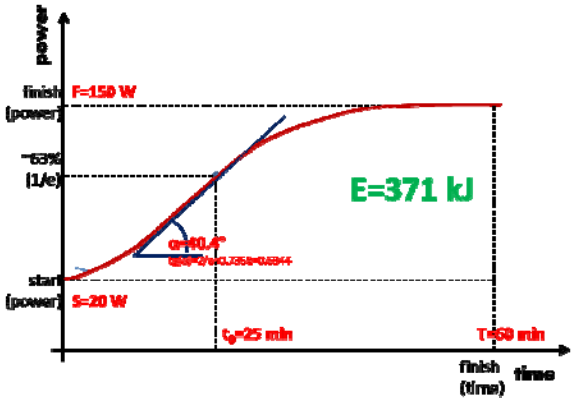
Figure 5. The inflexion point of Weibull function at $t=t_0$

Note, the Weibull distribution could be well approached by normal (Gaussian) distribution over a>2. In the Gaussian (normal) distribution the mean and the median are equally μ.

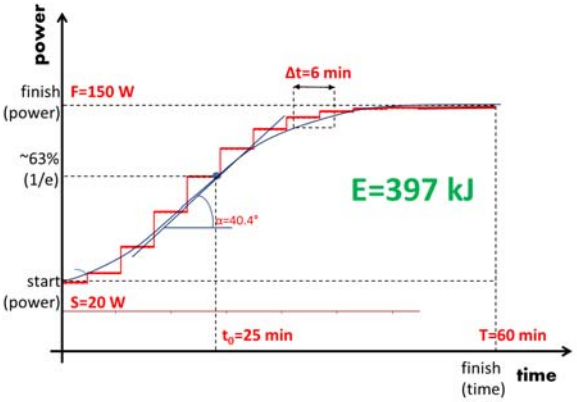
The area under the curve (shaded in the next figure) representing the complete energy-dose which is provided to the patient.



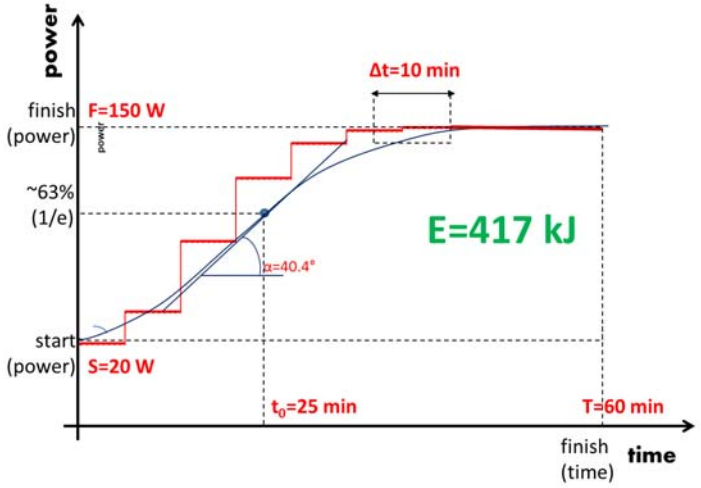
A certain realistic step-up treatment is shown below, S=20W, F=150W, T=60min, t_0=25 min, a=2 (α=40.4°). The obtains dose is 371 kJ.



However the continuous increase of the temperature does not fit to the homeostatic steady-state requests. Physiological response time (when the homeostatic equilibrium is reestablished after a definite disturbance) is 5-7 min. We propose at least 6 min on the definite chosen power level before the next increase step-up.
Considering this transient as 6 min, the step-up heating is shown below. In this case the obtained dose is higher due to the upfitting rule, which we applied.



In case of use 10 min relaxation time the protocol is shown below.



Important remarks about the dose

Difference between the poison and medicine is only the dose. Numerous committed suicides are performed by anyway useful medicine in lower doses. The dose is an important factor of efficacy safety and reproducibility too. In case of medication or radiation oncology we know the dose units as quantitative measurable values in mg/m^2 or J/kg in chemo- or radiotherapies, respectively. In hyperthermia the temperature is overemphasized as a dose, however it is not a quantitative parameter, it is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic average of the indivisual energies of the small units in the system. In chemo-therapy the cytotoxic remedies could cease very serious side effects, their safety has emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.
When the medication definitely has no side effects (or the side effects are handable) then the dose by their safety role has no upper limit, and also when the dose is limited but it is too high for the actual patient due to the biovariable poisioning limit, than the actually applied dose is of course lower, trying to fit it for the actual patient.
Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) sensing and note the toxicity limit: the heat-pain is immediately limits the oncothermia dose. When the preset dose is too much actually it has to be modified by the personal requests. On the other hand, when the preset energy-dose is too small (the patients actually can tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety and together with this for the efficacy too.

Oncothemia Consensus

Oncothermia became a widely used and popular method in over 15 countries of the world. It is not a “gold standard” yet, but it is on the way to reach its stable and important position as a “fourth column” among the main oncotherapy modalities. It has wide-range applicability for every solid

tumor in all possible localization, irrespective its primary or metastatic form. It could be applied together with all the known oncotherapy methods, and it is applicable in higher lines of the therapy protocols, even in the refractory and multirelapsed cases as well. Its applicability contains the curative and palliative approaches as well as it is well personalized to provide the optimal available treatment for the given case. A comprehensive book [19], and numerous scientific and technical papers were published on oncothermia, [20],so the technical basis is stable. Oncothermia has collected during its 21 year existence a massive expertise and large data-collection, which are the basic of any convention for treatment protocols. The main factors to fix a personalized protocol are (1) kind of the complementary treatment, [decisional basic is the protocol of the "gold standard" therapy], (2) kind of the tumor entity, (3) kind of the personal status (4) physiological factors of the patient. The most frequently applied bimodal treatments are the oncothermia combined with chemotherapy or radiotherapy, while in trimodality it is combined with the radio-chemo-therapy. Oncothermia works on **conduction principle**. RF-current flows through the patient from one electrode to the other one. Electrodes are flat-metals, both under water pillow: one is in the bolus; one is under the water-mattress. Water is a transmitter of the RF-current, making possible a good fit of the human body to the flat metals. Both water-electrodes (the water-bed and the water-bolus) are parts of the highly sophisticated electric circuit and not only a matter of convenience. The well-constructed device **does not radiate**, the RF-energy flows in a controlled way to the constrained directions, the current delivers the energy where the malignancy is. Both electrodes are active, current flows through them in all the frequency periods.

Oncothermia is a **personalized, non-toxic treatment.** Oncothermia, in most of the cases, is applied when the conventional cancer therapies fail, when the applied therapies need resensitizing or their substitution is necessary. Oncothermia efficacy is focused on patient-centered values: **survival time and quality of life**. Oncothermia can be applied as triple- or quadruple-modality (radio-chemo-thermo-therapy and additional to surgery (adjuvant or neo-adjuvant) as well as some supportive therapies (vitamins, enzymes, etc.) can be given alongside. Oncothermia is a versatile treatment for various solid tumors, its applicability is not limited to specialties, its universal applications could be easily fitted to all the "gold-standards" as well as it could be a good complementary support for other oncotherapies too.

Patient is a well-controlled part of a resonant electric circuit (see Figure 6.) and the current flow must not be blocked by any extra isolating layers (see Figure 7.)

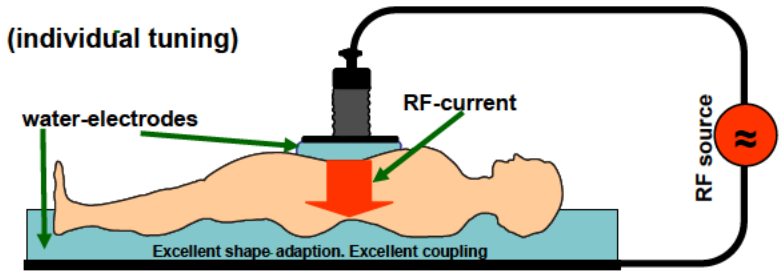


Figure 6. The patient is in a controlled circuit

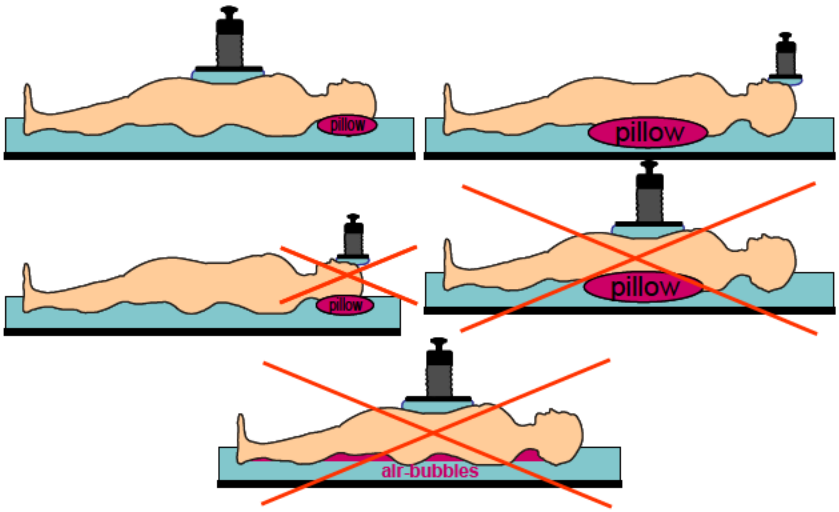


Figure 7. The current flow must not be blocked by any extra isolating layers

Oncothermia consensus for TREATMENT

1. Apply only in combination (exception if the conventional treatments are not applicable)
2. Treatment time is 45-90 min (average is 60 min)
3. Treatment frequency 2-3 times a week (sometimes everyday low-dose for blood-perfusion)
4. Treatment number 4-12/cycles (average 5.8)
5. Treatment cycle follows the combination (average is 2.3)
6. Step-up heating, gradually increased power, (follow the adaptability of the patient)

Give time to adapt the modulation (in case of sensitive organs like the brain). No blocking for current is necessary.

Oncothermia consensus for SAFETY

- Physician and/or trained clinical staff must be in duty and monitor permanently the treatments!
- The treatment needs extra care, when the patient has reduced thermal sensitivity!
- Treatment is prohibited when the patient is unconscious!
- Treatment is prohibited when patient is under deep-sedation or anesthesia!
- Treatment is prohibited in case of patient, who isn't able to communicate with physician!

Oncothermia consensus for PRACTICE

- If the patient has inclination to epilepsy, the physician has to take extra attention!
- Make pause of the treatment at rearranging and/or positioning the applicator!
- Clear away all metallic or magnetic pieces from the patients before the treatment!
- Check the well filled electrode bolus, do not work with air-bubbles!
- Control the frame of electrode out of touching the skin!

Protocols for combination with radiotherapy (RT) has to consider the blood perfusion of the tumor. When the tumor has adequate blood-perfusion then due to its high oxygen content it is sensitive for RT. In this case RT has to be applied first, immediately following by oncothermia with the highest tolerable power. This combination process is repeated every second day, (while the fractionated radiation could be on its own protocol every day). Oncothermia follows RT immediately (in 30 min range). In case of low blood-perfusion oncothermia has double role: increases the blood-flow to sensitize the RT and supports the cell-killing mechanisms. Fractionated RT follows oncothermia in this case in everyday application. In case of chemotherapy oncothermia has to be started when the highest chemo-perfusion is expected in the tumor-lesion to support the chemo-infiltration and the chemo-metabolism in the tumor. All the protocols have to be fitted to the request of the tumor-localization, and its duration has to be actualized by the stage and the progress of the cancer.

The electrode application for radio-oncothermia with high blood-flow and low blood-flow cases is shown in Figures 8., 9. The chemo-combination is shown on Figure 10. The radio- and Chemo-therapy sequences are shown on Figures 11., 12., 13.; while the sample protocols actually are shown on Figures 14., 15., 16.; respectively.

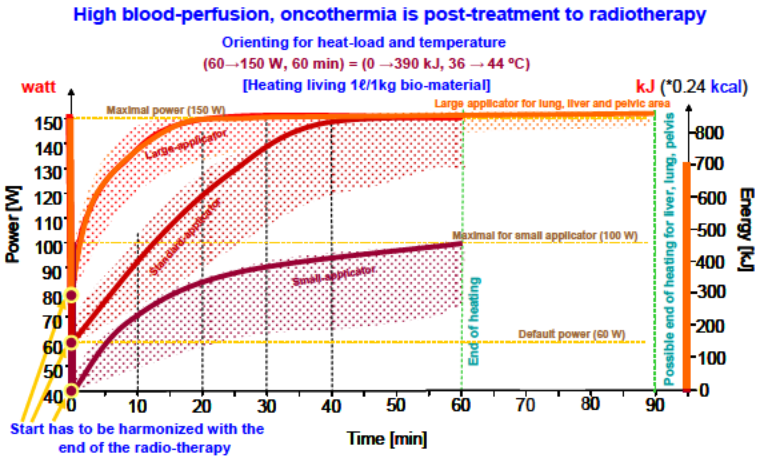


Figure 8. Applicator protocol for post-radio treatment

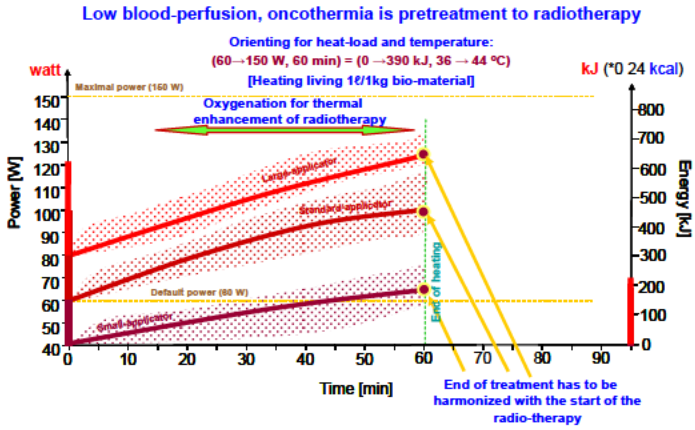


Figure 9. Applicator protocol for pre-radio treatment

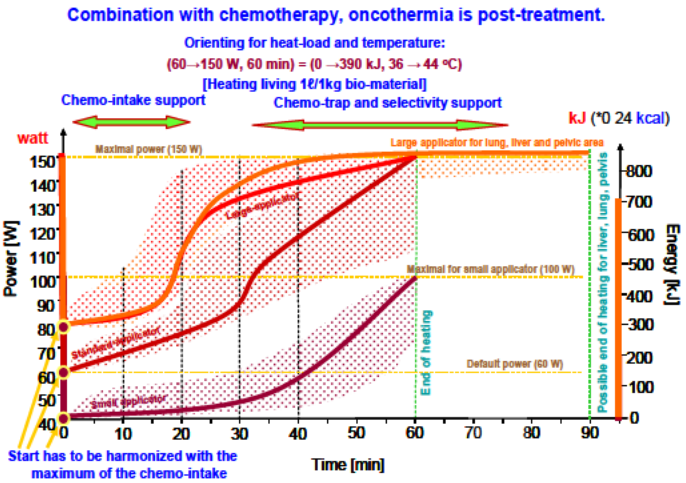


Figure 10. Applicator protocol for complementary chemo-therapy

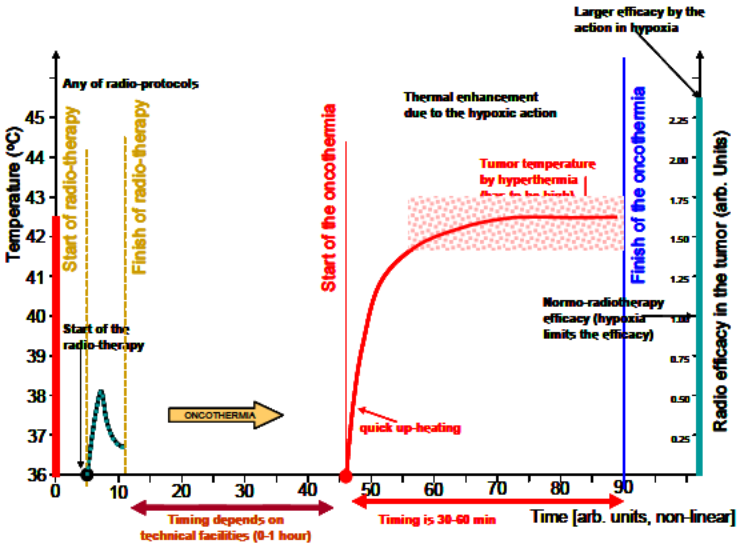


Figure 11. Sequence protocol for complementary radio-therapy, when the tumor has high blood-flow

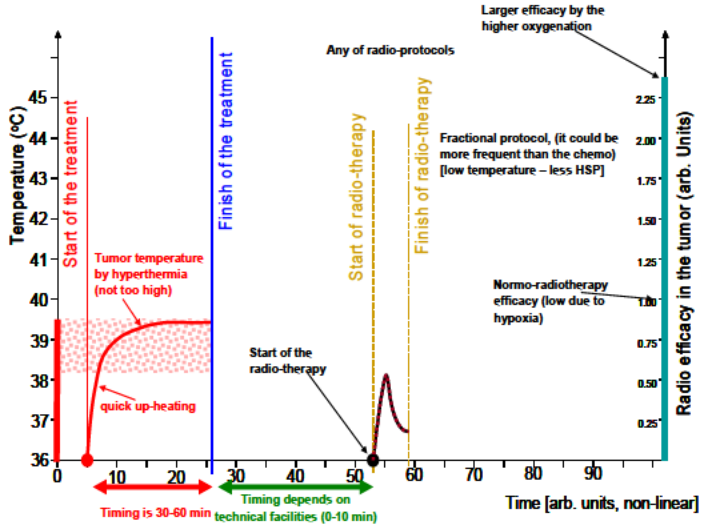


Figure 12. Sequence protocol for complementary radio-therapy, when the tumor has low blood-flow

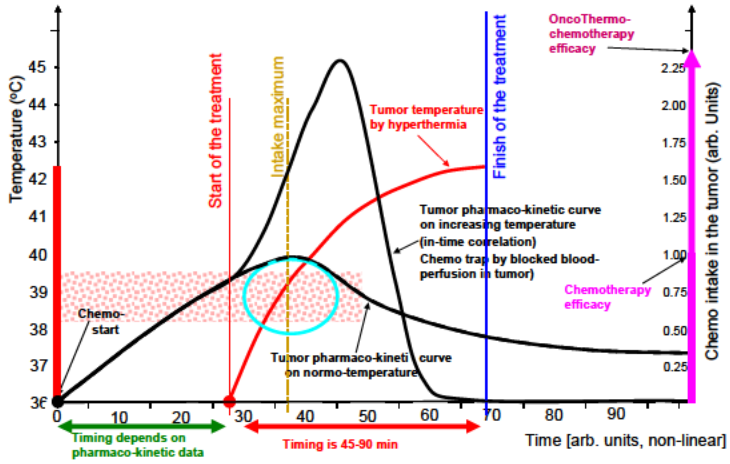


Figure 13. Sequence protocol for complementary chemo-therapy

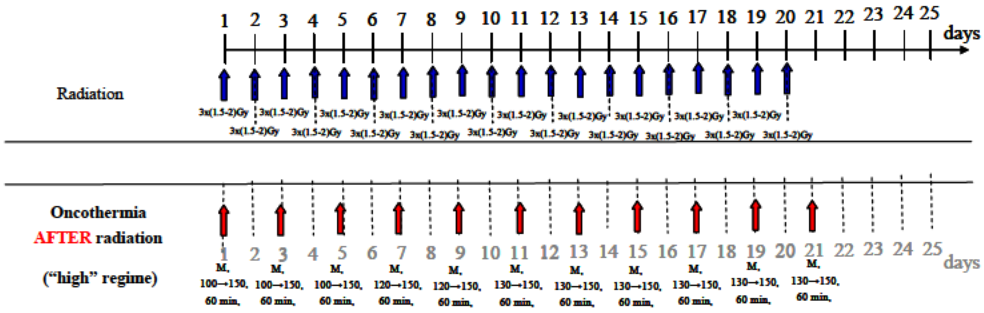


Figure 14. Sequence protocol for complementary radio-therapy, when the tumor has high blood-flow. In case of high blood-perfusion the radiotherapy efficacy is expected high, its primary application is desirable. Oncothermia has to be applied afterwards with the highest tolerable dose to achieve the maximal result

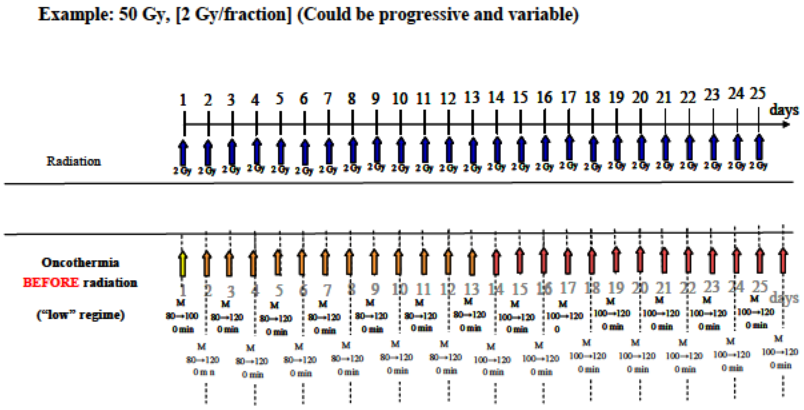


Figure 15. Sequence protocol for complementary radio-therapy, when the tumor has low blood-flow. In case of low blood-perfusion the radiotherapy efficacy is expected low. The primary application of oncothermia is desirable, with low power making the oxygenization effective. Radiotherapy has to be applied afterwards

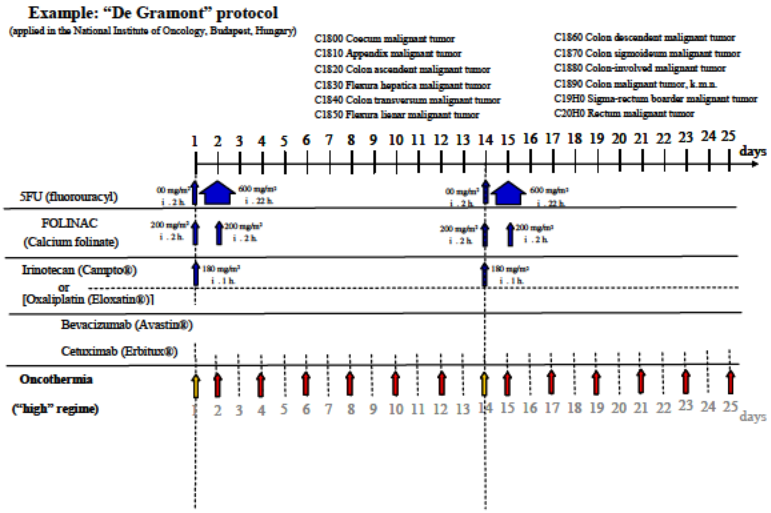


Figure 16. Sequence protocol for complementary chemo-therapy, when the tumor has high blood-flow. In case of chemotherapy has to be fitted to the chemo-metabolism and pharmacokinetics of the actually applied drug. Oncothermia has to be applied before or during the chemo treatment. Administering the chemotherapy after the hyperthermia could decrease the chemo-intake of the tumor, due to the fact that hyperthermia blocks the neoangiogenetic blood-flow. Best performance of the combination can be achieved, when the oncothermia is performed at the time when the given drug has the highest chemo-dose by the tumor. These kinetic data of the actual drug are usually provided by the producer

Agents	Dose [mg/m²]	Day of treatment																	
		1	2	3	4	5	6	07	8	9	10	11	12	13	14	15	16	17	18
Cisplatin	15	+							+							+			
Gemzar	600	+							+							+			
Oncothermia	A2P	+			+				+			+				+			+

*Figure 17. An example of chemo-protocol when oncothermia is applied during (simultaneously, concomitant) to the chemo treatment it has to be fitted to the chemo-metabolism and pharmacokinetics of the actually applied chemo. Give it when the maximal chemo infiltrated to the tumor. In continuation (between the chemo-cycles), give it 2-3 times a week.. Course: 18 days, Interval between courses: 7 days, Diagnosis: C25: Malignant neoplasm of pancreas, * A2P – according to the protocol for this localization. (Russain standard by Dr. S.Roussakow)*

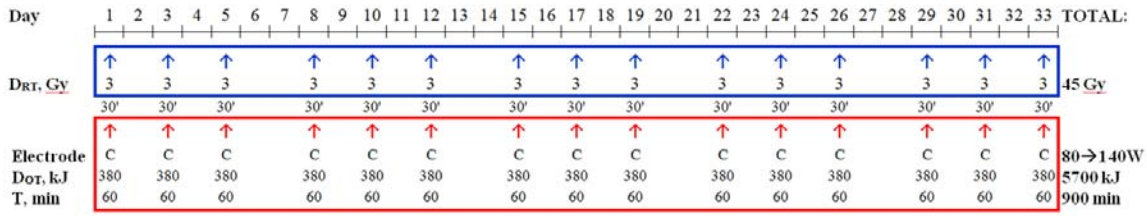


Figure 18. Synergy with hypofractionated RT with medium fractions: RT protocol: TD=45 Gy, SD=3 Gy with 1 day interval; OT protocol: Standard Applicator, 80→140W (380 kJ) 60 min with 1 day interval; Modification of every RT dose; RT→OT with interval <30 min (Russain standard by Dr S .Roussakow)

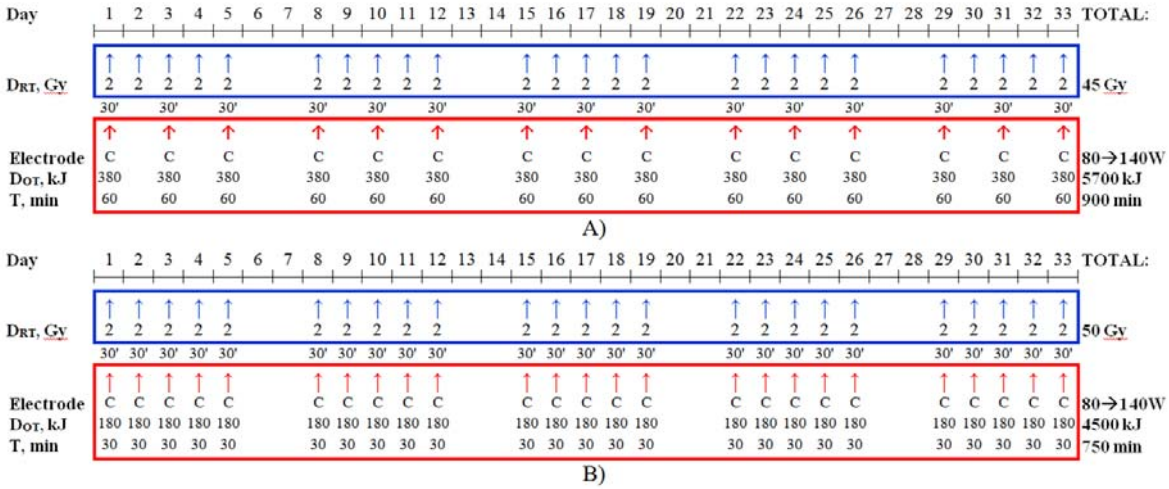


*Figure 19. Potentiation of fractionated RT with small fractions: (TD=50 Gy, SD=2 Gy daily). **OT protocol A**: Standard Applicator, 80→140W x60 min (380 kJ) with 1 day interval. Modification of every second RT dose. RT→OT with interval <30 min. **OT protocol B**: Standard Applicator, 80→140W x30 min (180 kJ) daily. Modification of every RT dose. RT→OT with interval <30 min (Russain standard by Dr. S.Roussakow)*

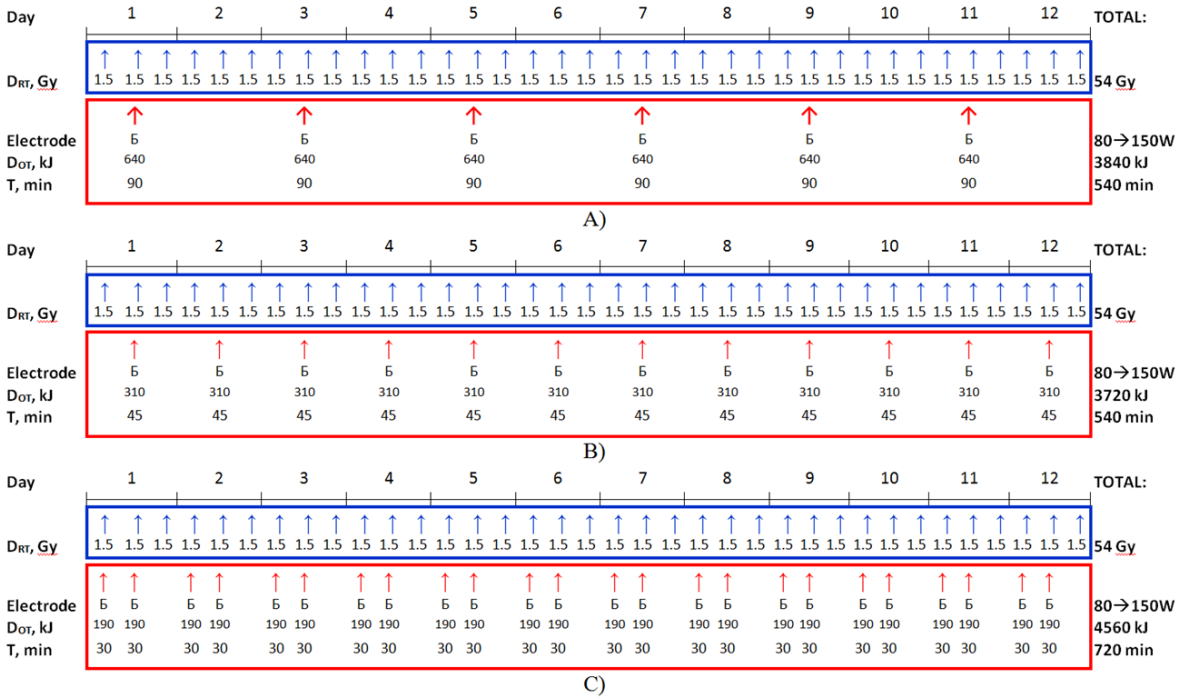


Figure 20. Modification of hyperfractionated small-fractions RT protocol (CHART, lung cancer, 54 Gy for 12 days, SD=1,5 Gy 3/day): A) standard OT (SD); B) fractionated OT (½ SD); C) fractionated OT (⅓ SD). (Russain standard by Dr. S. Roussakow)

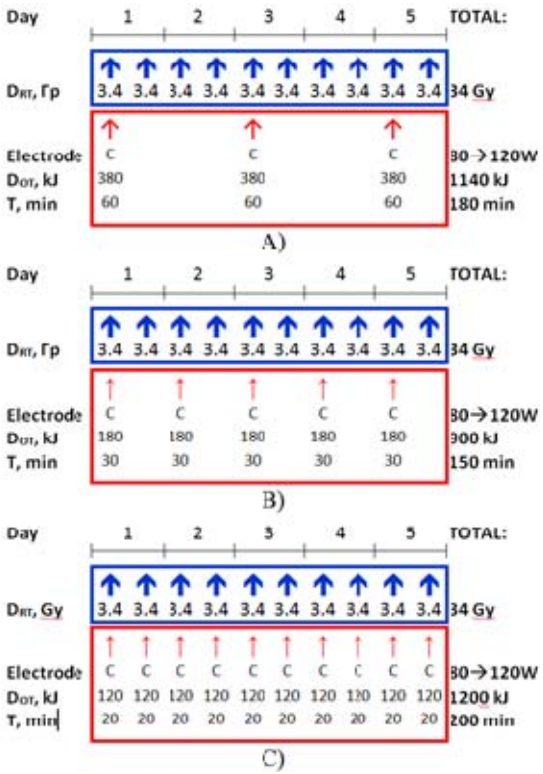


Figure 21. Modification of hyperfractionated big-fractions RT protocol (APBI, breast cancer, TD=34 Гр for 5 days, SD=3,4 Gy 2/day): A) Standard OT (SD); B) fractionated OT (½ SD); C) fractionated OT (⅓ SD). (Russian standard by Dr. S. Roussakow)

RT fractionation	RT/OT frequency	Duration of OT session		
		%	30 cm	20/10 cm
Hypo fractionation	Interval 1 day or more	100%	90 min	60 min
Normal fractionation	Daily	50% (1/2)	45 min	30 min
Hyper fractionation	> 1 per day	33% (1/3)	30 min	20 min

Figure 22. Standard OT session could be applied with 2 or 3 fractions. Fractionation allows to use OT with every single RT dose for more efficient potentiation. The rationale of OT fractionation is based on non-thermal nature of OT effect which allows to dose OT by energy. The total effect of fractionated OT could exceed the effect of standard OT session because: (1) During short session, heating phase is relatively longer and trans-membrane thermal gradient is relatively higher. (2) Clinical data showed that the main predictor of OT effect is number of treatments (Russian standard by Dr. S. Roussakow)

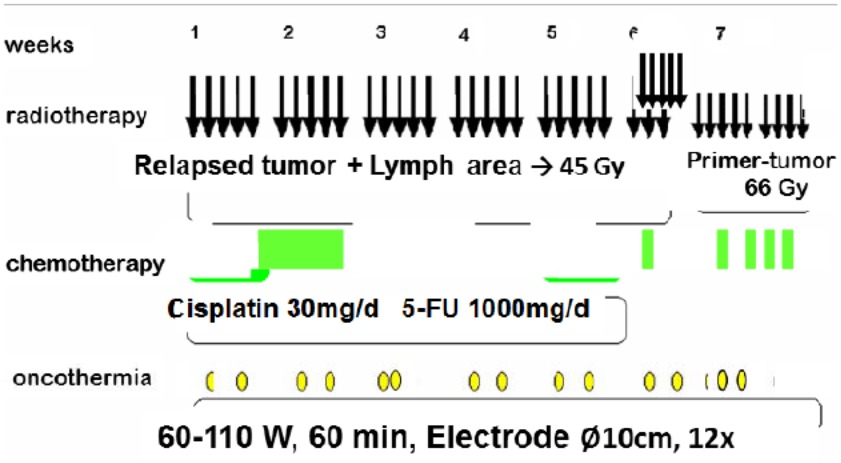


Figure 23. Example of trimodal protocol. Investigator: Prof.H.Renner, Instutute: Klinikum Nord, Nürnberg, Germany, Patient: H.K., 49 y, male,Primer-tumor: esophagus, diagn.02/03; Histology: Squamous cell carcinoma G3, Resection – Relapse: 06/05, inoperable Metastases: multilocal lymph node; Result: Complete remission (CR) Follow-up: after 30 month tumor-free

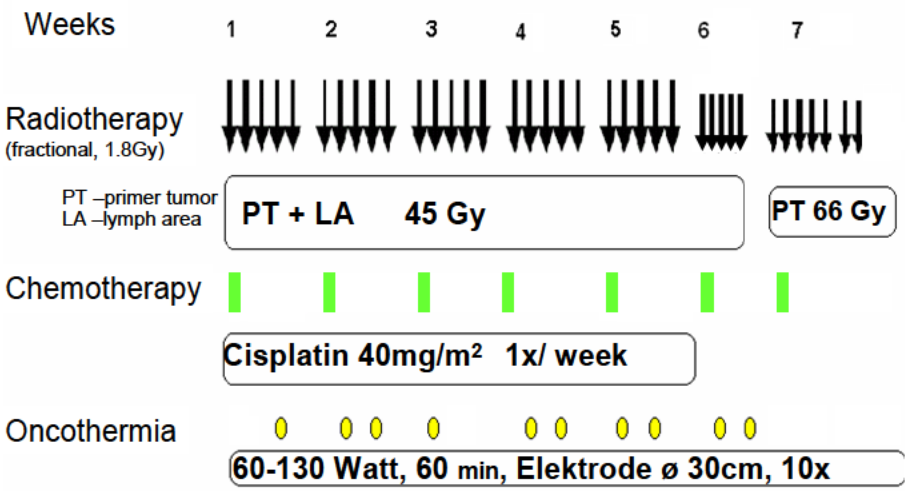


Figure 24. Other example of trimodal protocol. Investigator: Prof.H.Renner, Institute: Klinikum Nord, Nürnberg, Germany, Patient: G.U., 50 y, male, Primer-tumor: Esophagus carcinoma, inoperable; Histology: Squamous cell carcinoma G3; Metastases: in mediastinum & celiac ganglia Tumor-classification: cT2 cN1 M1a G3 R2; Result: Complete remission (CR) Follow-up: after 12 month tumor-free

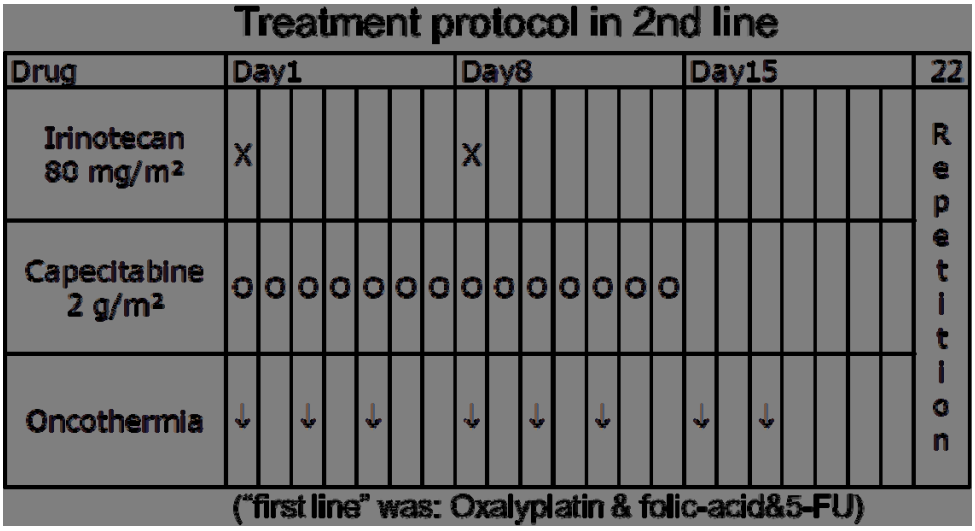


Figure 25. Investigator: Prof.H.Kirchner & Dr.P.Panagiotou; Department: Department of Hematology & Oncology, Hospital Siloah, Hannover, Germany, Published: Panagiotou P, Sosada M, Schering S, Kirchner H: Irinotecan plus Capecitabine with regional electrohyperthermia of the liver as second line therapy in patients with metastatic colorectal cancer; ESHO, 2005, Graz, Austria

Side effects

- Light erythematic redness (<8%)
- Surface burn (very rare)
- Adipose burn (<3%)
- N.B. Not gains (mostly suppresses) the side-effects of other complementary applied therapies.

Contarindications

- Organ transplants or vanished immune-reactions
- Missing thermal sensing
- Inability to communicate
- Woman in pregnancy
- Pacemaker or other electric implants (?)

High care is necessary

- Epileptic of electric sensitivity
- Ascites or other free-electrolytes
- Large metallic implants

Sedation, analgesia or anesthesia is not allowed when oncothermia is applied!
Oncothermia is applicable in most of the cases, when normal heat-therapies are not. and it is applicable in hopeless cases for the gold standards

Control and check of the results

A new control is emerging, which oncothermia uses in wide range: the OMICS. Mainly we apply proteomics, the appropriate tumor-markers.

Examples are on the following figures:

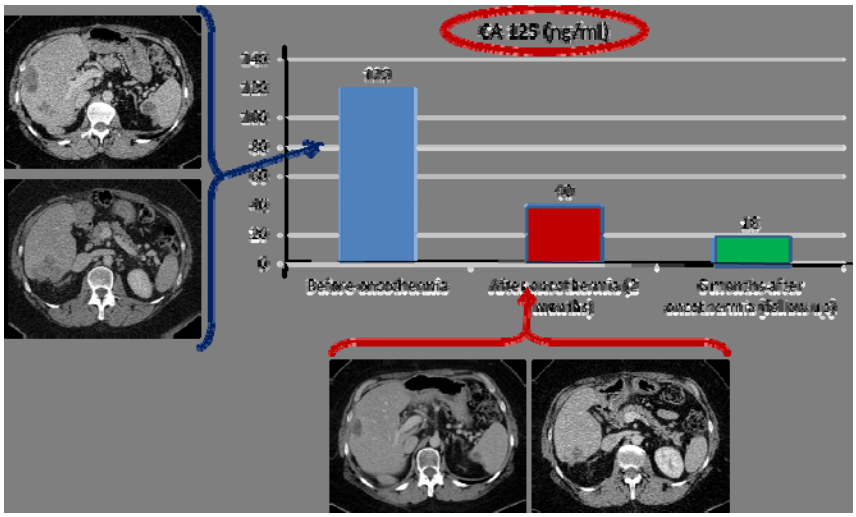


Figure 26. Investigator: Dr. W-P. Brockmann, Institute: Institute OncoLight Hamburg, Germany, Patient: 51 y, (G.K. ♀), Diagnosis: Ovary carcinoma, + liver & spleen metastasis, Therapy : oncothermia + radiation therapy + operation + dendritic cell treatment Result: Partial remission

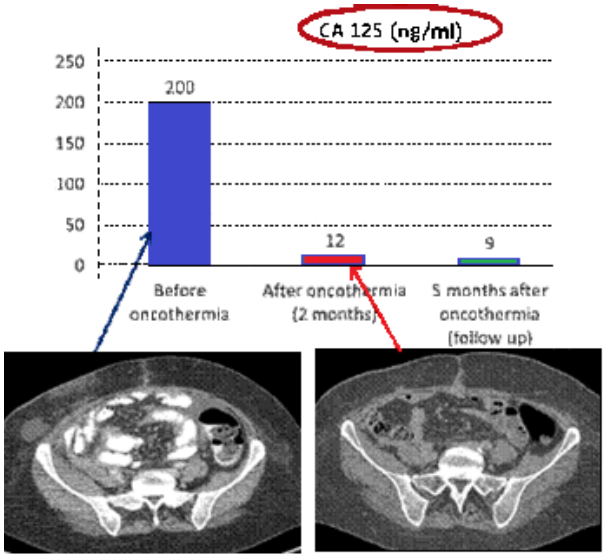


Figure 27. Investigators: Dr. W-P. Brockmann Institute: Dr. W-P. Brockmann Institute OncoLight, Hamburg, Germany. Patient: GK. 51 y female, Primer-tumor: Ovarial-Ca with liver and spleen metastases, Treatment: Radiotherapy 2x/day + local dendritic cell thepay + oncothermia

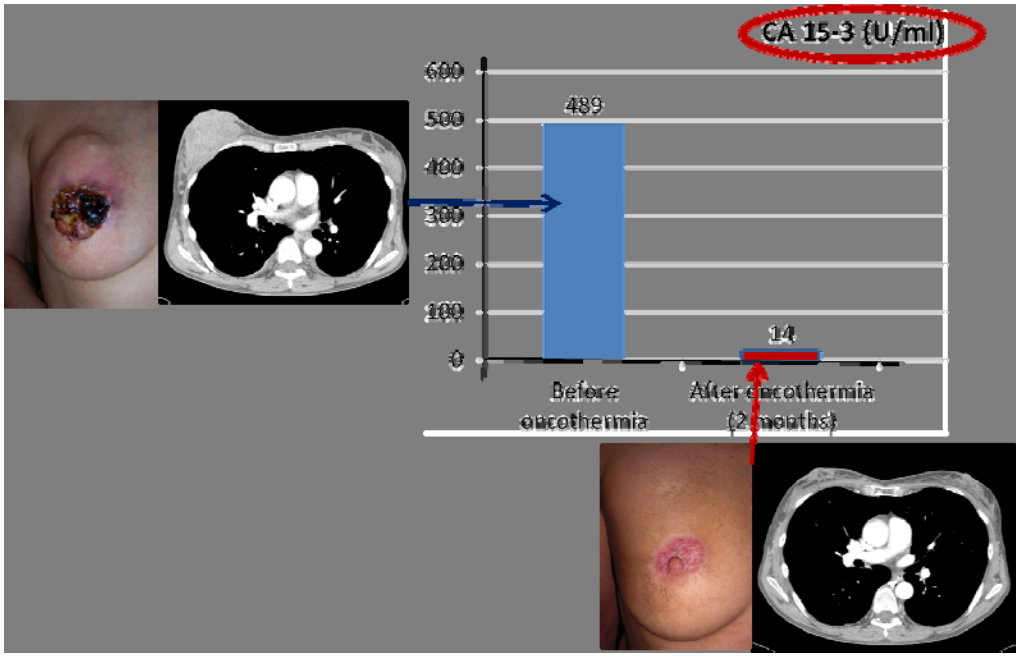


Figure 28. Investigator: Dr. W-P. Brockmann, Institute: Institute OncoLight Hamburg, Germany; Patient: 51 y, (M.S., ♀) Diagnosis: Mammary Carcinoma >10 cm, Therapy : Radiation therapy (2x) + oncothermia + WBH + Mitomycine C; Result: Complete remission

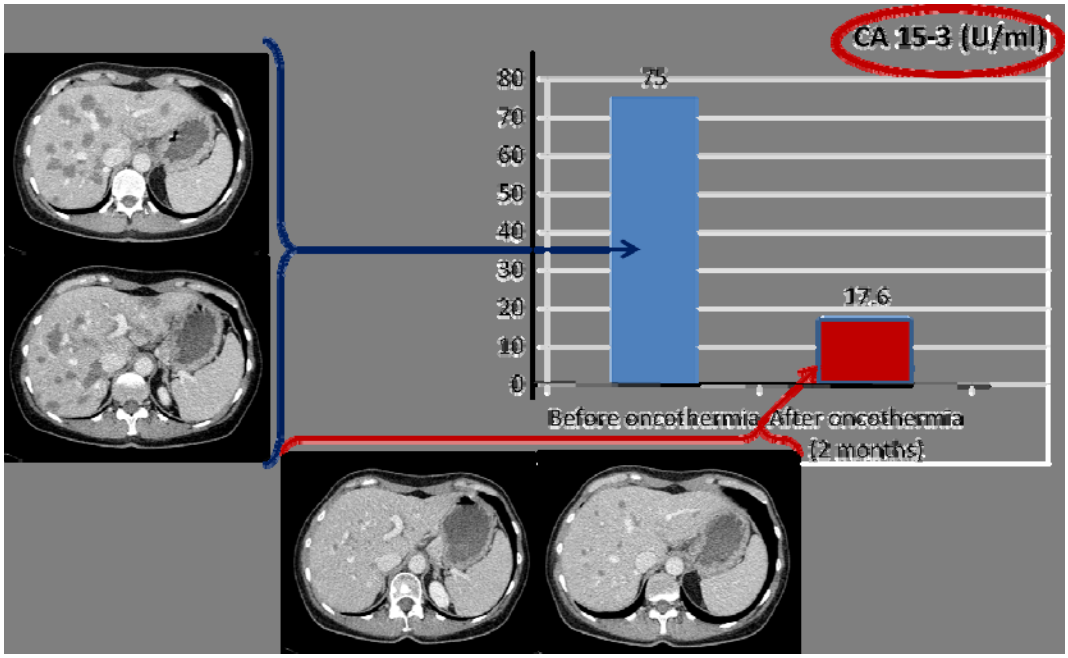


Figure 29. Investigators: Dr. W-P. Brockmann Institute: Dr. W-P. Brockmann Institute OncoLight, Hamburg, Germany. Patient: 58 y, female. Primery-tumor: Mammary CA with liver metastasis, diagnosed; Treatment: Radiotherapy, whole-body hyperthermia, oncothermia, and local dendritic cell therapy Result: partial remission

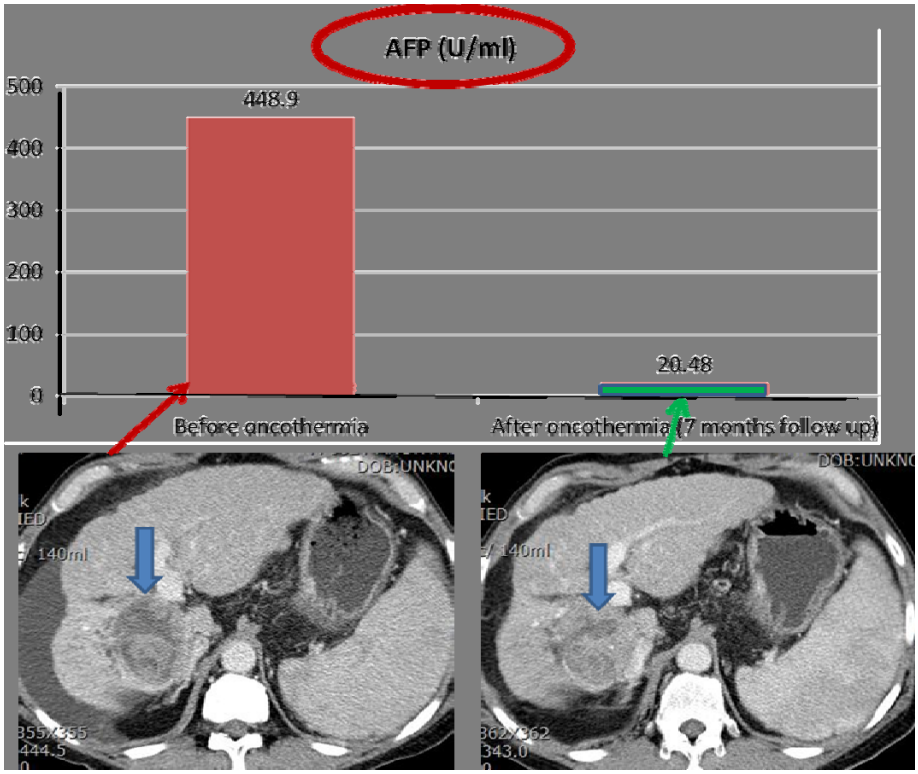


Figure 30. Investigator: Prof.Dr.Taesing Jeung; Institute: Department of Radiotion Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital. (61y/M), HCC & TACE, Oncothermia 24 times; Published: 31st ICHO Oct. Budapest; 2012

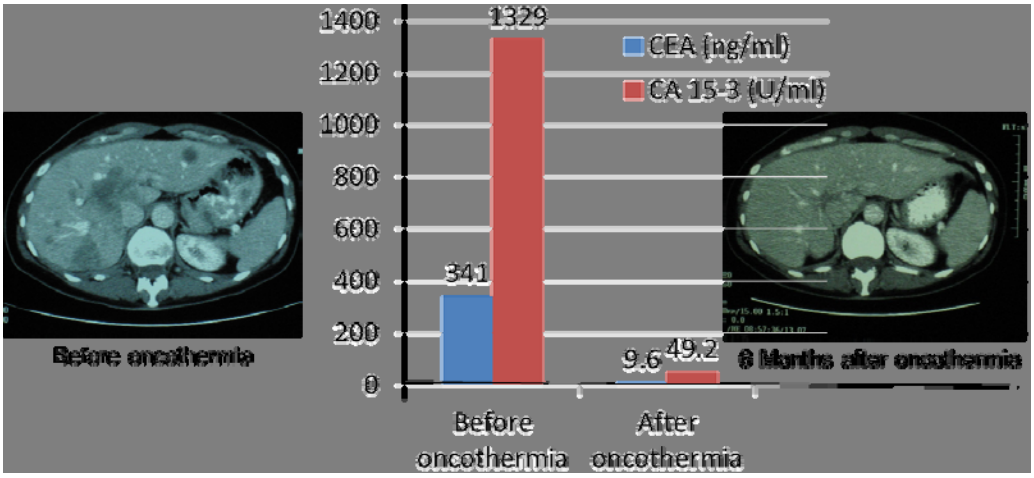


Figure 31. Investigator: Prof.Dr.A.Herzog; Institute: Fachklinik Dr.Herzog, Nidda, (Bad Salzhausen), Germany; Patient: 43 y, female, (M.M.); Diagnosis: Mammary carcinoma, (fieve years earlier than the hepatic metastasis was diagnosed). Symptoms: liver pain, weakness. GOT 202 U/l, GPT 255 U/l, γ-GT 508 U/l; Prior therapy: adjuvant FEC 5 years earlier (HR negative, HER-2-pos). Treatment: reduced dose intensity of vinorelbine + Herceptin, accompanied by several sessions of oncothermia of the liver, Result: complete remission (CR); absence of pain, transaminases within normal limits

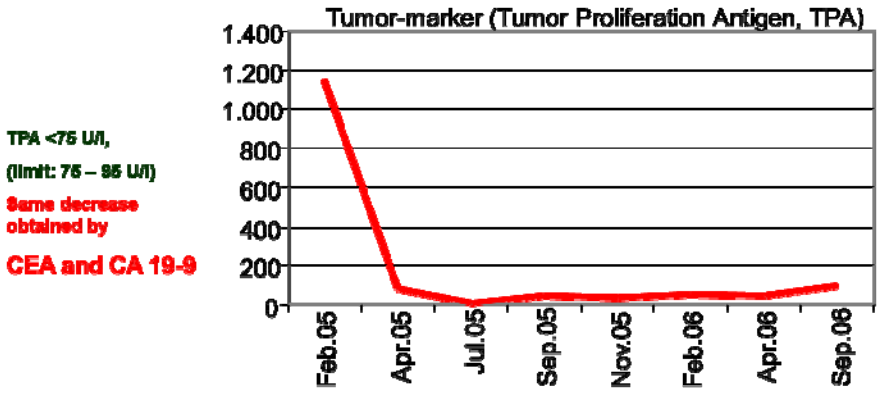


Figure 32. Investigator: Prof.H.Kirchner Department: Department of Hematology & Oncology, Hospital Siloah, Hannover, Germany. Patient: K.L. 69 y, male; Diagnosis: Uroepitheluum carcinoma, Mar.2004, Surgery: Nephroureterectomy, Tumor-classification: pT2 N0 Mx R0 G2; (Feb.-Aug.2005). Metastasis: multiple hepatic; Therapy: Gemcitabine / Cisplatin (3 session) + oncothermia (Liver) followed by PNP Gemzar / Carboplatin (4 session); Result: Good partial remission (PR) tumor and tumor marker regression (<1cm) (Aug.2005-Jan.2006) Follow-up: Jan.2006-Sep.2006 excellent status, disease free. Oct.2006 Rezidiv paraaortale lymph-nodes, liver collapse, exitus

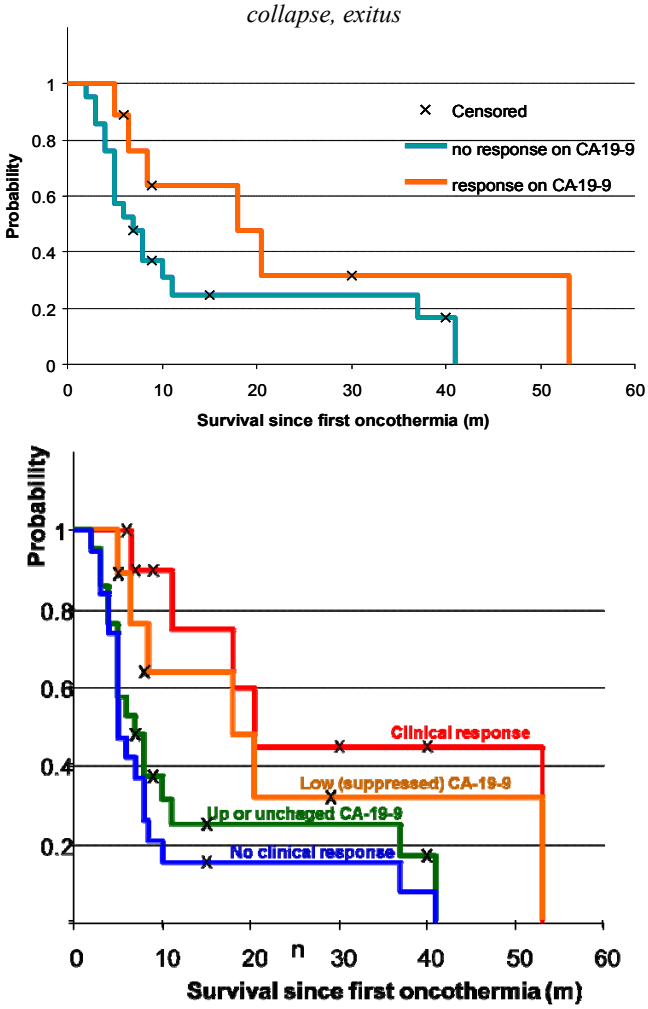


Figure 33. Comparison of the survival time and the tumor-marker indication of the patient for pancreas tumor. Douwes F. (2004) Thermo-Chemotherapie des fortgeschrittenen Pankreaskarzinoms. Ergebnisse einer klinischen Anwendungsstudie. Douwes F. Migeod F. Grote C. (2006) Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und einer Zytostase mit Mitomycin- C und 5-FU

Characteristics

Oncothermia is a safe process. Oncotherm devices work actively in over 100 places worldwide. During their twenty years no serious side effects were reported. Due to its special focusing and efficacy, the applied power could be low. The safe treatment could be shown by near-eye cases also, [21].
Oncothermia is applicable for the treatments in 3rd-line and over, even it is a palliative tool in hopeless cases [22]. Most of the cases show a resensitizing of chemo- and/or radiotherapies. Such high-line treatments have very few evidence based trials in the literature.
Oncothermia has safely operated equipment's, completely checked according to European Medical Device Directive. While for HRF treatment heavy shielding is necessary, oncothermia does not need it. The EMC category is Class B, which allows using this equipment safely in homes and living areas also.
Oncothermia is a new reliable technique [23]. It is easy to use and cheap, which could optimally fit to both the patient's possibilities and the budget of the social insurance. Its requested space is one third of the classical hyperthermia applications, its price is one sixth of the classical hyperthermia applications, its human operating resource is only a trained nurse, its treatment capacity is (7 patients)/(8 hours).
Application of oncothermia is entirely legal. According to European Medical Device Directive (MDD) oncothermia is certified by TUV, Munich. All the devices are manufactured according to the ISO 9001 and ISO 13458 standards. The marketing and sales processes are certified by Notified Body SGS according to ISO9001 standards.

Is Oncothermia trustful method for oncologists?

Oncothermia is a well-established method worldwide [24]. Certificates, which were reached in various continents and different countries, are based on the high level research data and the clinical studies completed and performed by the Oncotherm company during its twenty years activity. The method technically is well established [20] and addresses multiple, new and important topics from laboratory use to the clinical applications, [25].
Oncothermia had formulated a new paradigm [26], and made a pioneering job: it was the modulated electric field application, which later had good continuation in the literature in many laboratories worldwide. Its definite breaking results were on the modulated field effect combined with the thermal actions [27], showing large development in the present clinical practice. The electric field action was considered in serious manner in 2000 by Nature [28], and has been intensively applied in the clinical practice [29], [30].The modulated electric field actions were applied for various accepted clinical trials [31], [30].
The second new approach was the controlled micro-heating, [32], which makes possible to introduce the dose as the absorbed power [33], [34]; like it is used in the standard radio-therapy as well.
The third new important field which was pioneered by oncothermia is the immune-simulative applications of the modulated electric field, showing the definite natural apoptotic cell-killing [35], [36] with activation of various leucocytes [37] to isolate [38] and kill the malignant lesion.
The fourth pioneering field is the [39] abscopal (bystander) effect of modulated electric field. According to the remark of world-famous tumor vaccination researchers in their last conference, it could be a good basis to be involved in this very modern and promising field. This effect makes a great opportunity to make the local treatment systemic [40], like the locally observed tumor became systemic by its malignant progress.
In clinical point of view Oncothermia makes also important and unique steps to go forward with proving its trustful performance [41]. It has various levels of clinical evidences, has multiple studies including phases of the data development from the toxicity measure (Phase I), [42],[43], through the efficacy (Phase II) [44], and the wide range clinical applications (Phase III/IV) [45]. Oncothermia has many retrospective studies but also many prospective ones in Phase II and Phase

III categories. The retrospective data are compared to the large databases, and compared to the multiple clinical institutions, making statistical evidences of the validity of the data.
Presently altogether oncothermia has 44 clinical trials involving 2326 patients from five countries (Germany, Hungary, Italy, S. Korea, China). These trials are covering 19 lesions: Bone (metastatic) [46], [47]; Breast [48]; Colorectal [49], [50], [51], [52], [53]; Gliomas [54], [55], [56],[57],[58]; [59], [60], [61], [62],[63], Esophagus [64]; Brain (metastatic) [65], Kidney [66]; Liver (primary) [67], Liver (metastatic) [68], [69]; Lung (NSCLC) [70], [71]; Lung (SCLC), [72], [69], Pancreas [73], [74], [75], [76], [77]; Pelvic, Gynecology, Stomach. Maximal patient number in a Phase III study was 311 (non-small-cell lung cancer). The average oncothermia enhancement ratio (ratio of the median survival of responders to non-responders) was 5.1. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.
Presently one large randomized clinical study is in progress (Mammatherm, www.mammatherm.de) and three are in the phase of the Ethical Committee (advanced, relapsed ovarian cancer, advanced relapsed pancreatic cancer and advanced relapsed cervix cancer). Multiple preclinical studies are in progress in various university research centers, including Universities in Germany, Hungary, S. Korea and Japan.
Oncothermia has good clinical achievements in the clinical studies, making stable basis of the clinical applications in various advanced primary and metastatic malignancies and giving the long time expected stable standard on oncological hyperthermia.

Is the Oncothermia application legal?

Everybody is interested to have legally safe business. In medical field it is even more important than any of other kind of businesses. The physician's responsibility in ethical and legal points is very high. The medical entrepreneur has great risk if the background is not stable enough behind. Using a treatment device in oncology is a category of such risk. The proper market approval is the CE certificate according to the European medical device directive (MDD). This is mandatory of course. However OncoTherm offers much more: solid scientific basis by university laboratories and research institutes, twenty years experience in many European and Asian countries (presently more than 100.000 treatments are provided yearly by oncothermia worldwide) and high ranked safety record without any serious side effect during these years. The very dynamic scientific and medical activity of Oncotherm is known in the scientific community by many publications and accepted results. We are pioneering the electromagnetic treatments in oncology. The modulated electric field with RF carrier frequency of oncothermia is a leading method in oncologic hyperthermia by its treatment number in all over the world. We are very active at all the international forums and conferences to make conditions risk-free and safe, insure your patients and your business also safe.
Oncotherm is seriously considering the legal protection of its customers. The main legal points are connected to the device market approvals (CE according to European Medical Device Directive) and the production standards (ISO13485, ISO9001). But this is far not enough! Oncotherm understood the request of the evidences of the working method, of the theoretical basis and of the medical efficacy. We are very pleased to announce such a long list of publications which was made in our twenty years experience by the method. We understood that the idea of "hyperthermia" is not enough for the proofs. Many hyperthermia systems exist, even many capacitive coupled too, but all of these have to prove their efficacy individually, because the technical differences could make huge deviations in their medical effects. Oncotherm makes intensive research, spends huge resources to make sure the referred effects and make our customers insured about the oncothermia method. We participate in many conferences and intensively connected with numerous Universities and research Institutes to make sure the effects and implement further developments of the method according to the latest biomedical and technical results. We are more than happy to share with our customers

our results and we are ready to give them all available help if necessary to prove the serious approach of our common oncothermia method.

Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat-flow on the membrane supported by the electric field effects). It is natural, it is not against the homeostasis, physiology does not work against the action. The main task is to direct the physiology in the standard way, and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium have to be stopped. Oncothermia follows the update demands of the modern oncology:

- It is a personalized therapy,
- It is non-toxic,
- It elongates the survival time of the patients,
- It completes the curative actions with increased quality of life,
- It has good cost/benefit ratio.

What are the limits of the old hyperthermia approach? (New paradigm is necessary for oncology.) The introduced new paradigm by oncothermia solved the classical challenges:
■ **Challenge (1)**: "The biology is with us while the physics is against us" (Overgaard J., [78]).
✓ ***Oncothermia solution:*** "The biophysics is with us"
■ **Challenge (2)**: "The biology and the physics are with us while the physiology is against us" (Osinsky S., [79]).
✓ ***Oncothermia solution:*** "The fractal physiology is with us"
■ **Challenge (3)**: "Reference point is needed!" (Fatehi D. van der Zee J., et. al. [80].
✓ ***Oncothermia solution:*** "Back to the gold standards, use the energy instead of temperature"

The task for future are challenging, and we are expecting professionals repeat our results and coming with us to fight in the war against cancer [81].

Concensus summary

Oncothermia has protocols for orientation of the treatments. The protocols however are orienting forms, and the actual treatment must be personalized and well-tailored on the patient and the conditions of the lesion, considering the sensing of the patients. One of the main orientations has to be the stressless treatments and the complete fit to the lesion. The oncothermia approach is a vivid way solving the old-problems in hyperthermic oncology: it is a controlled, reproducible and reliable treatment-modality. Oncothermia is a perfect candidate becoming the stable fourth column of conventional oncotherapies.

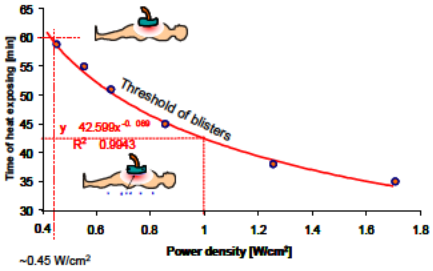
- ✓ **Apply first the "gold standards" and use oncothermia when others fail alone. (refractory, relapsing, inoperable, low blood-counts, psycho-resistance, etc.)**
- ✓ **Apply only in combination (exception if the conventional treatments are not applicable)**
- ✓ **Treatment cycle follows the combination (average number is 2.3)**
- ✓ **Treatment number 4-12 in one cycle (average 5.8)**
- ✓ **Treatment time is 45-90 min (average is 60 min)**
- ✓ **Give time to adapt the modulation (in case of sensitive organs like the brain)**
- ✓ **Treatment frequency 2-3 times a week sometimes everyday low-dose for blood-perfusion)**
- ✓ **Step-up heating, gradually increased power (follow the adaptability of the patient).**

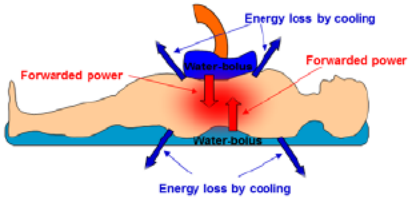
Oncothermia – personalized treatment option

Objective

The personalization of the oncological treatments is the new trend in modern medicine [82]. Oncothermia is a personalized treatment by tuned energy delivery to the targeted tumor [83]. This energy is well focused on cellular level [84], and makes the dose of energy optimal for cell destruction [85]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized. [86]

Introduction

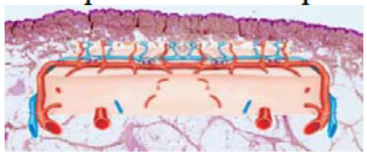


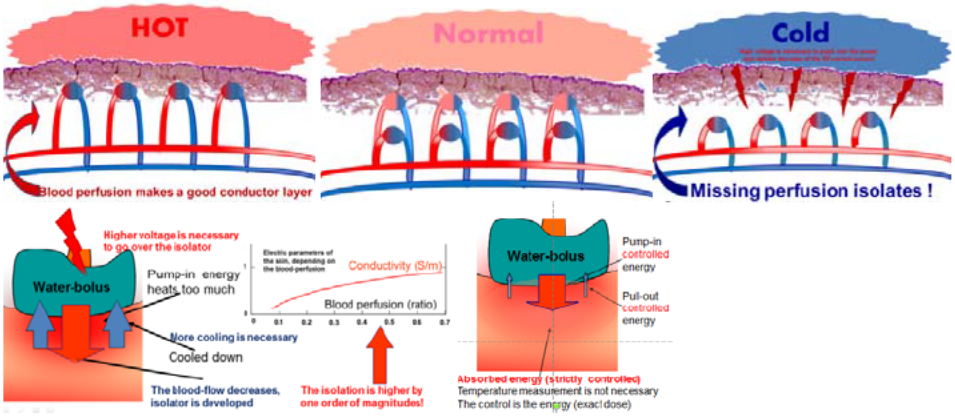


When the energy taken away by cooling and by the bolus is high and uncontrolled, than no control on the treatment as well.

Discussion

The main factor of the homeostatic control is physiological, based on the active homeostatic control of the blood-perfusion and blood-flow regulating the energy-intake and heat-exchange in the target. The high blood-flow is an effective heat-exchanger, cools the given volume. The well conducted treatment optimizes the current flow-density through the lesion, and optimizes the treatment. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. This regulation is also stress dependent, and depends on the human race-variants as well. The step-up heating is important not only avoid the inconveniences, but regulate the adaptation mechanisms. Healthy cells can be adapted to the electric/heat-stress, while this adaptation is much less in the malignant lesions. The applied step-up heating supports the physiological selection and makes the contrast of the reaction definite. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed for all the deep-seated treatments of various organs.

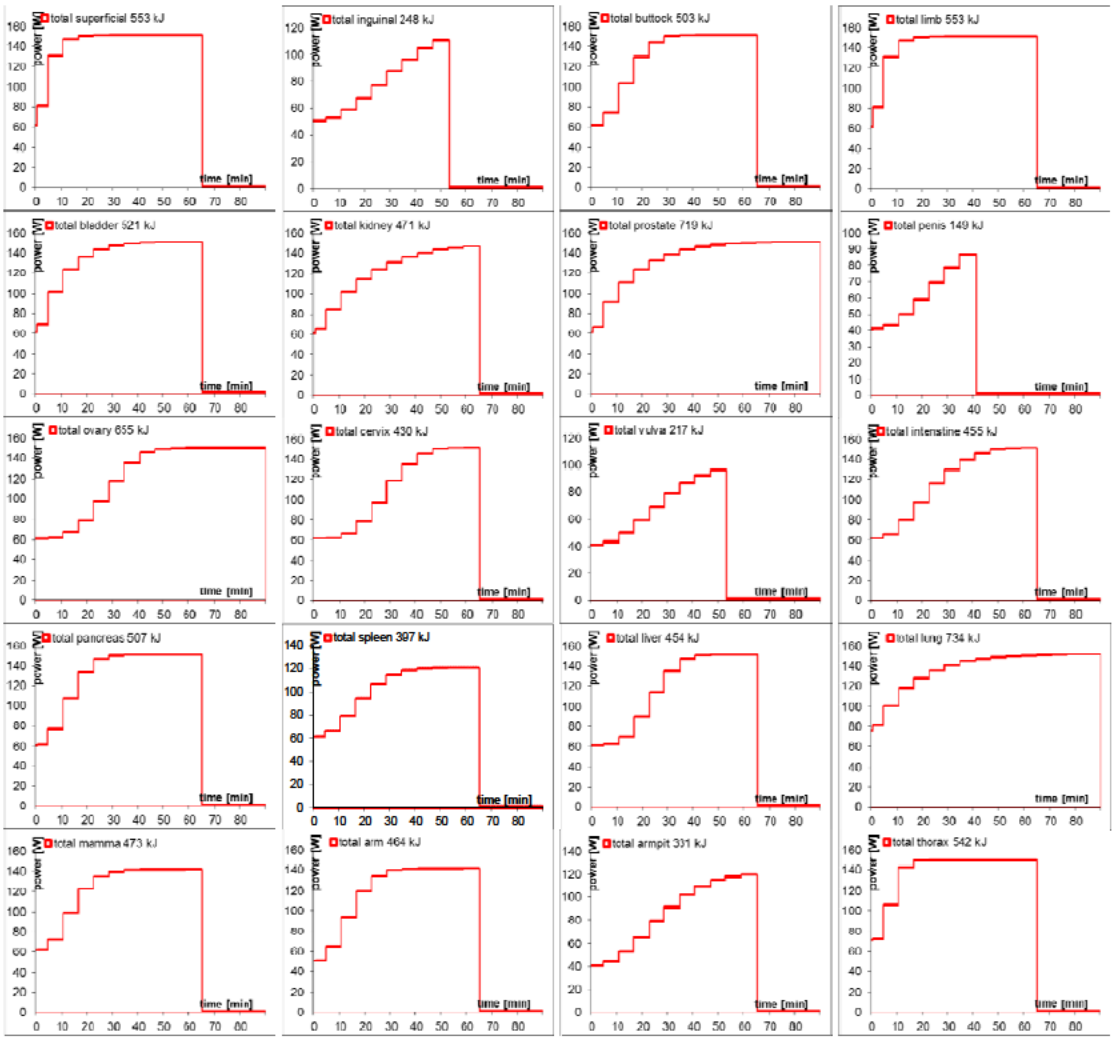


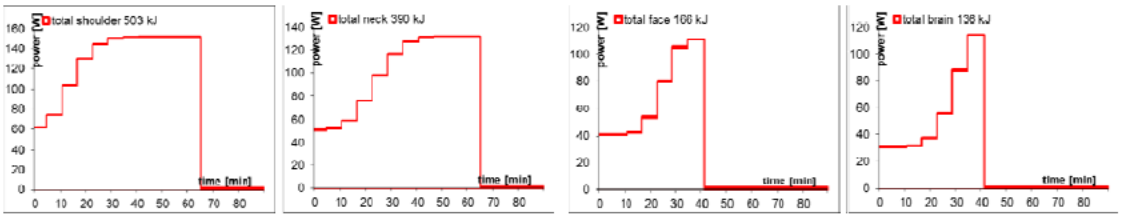


This patented technique makes possible

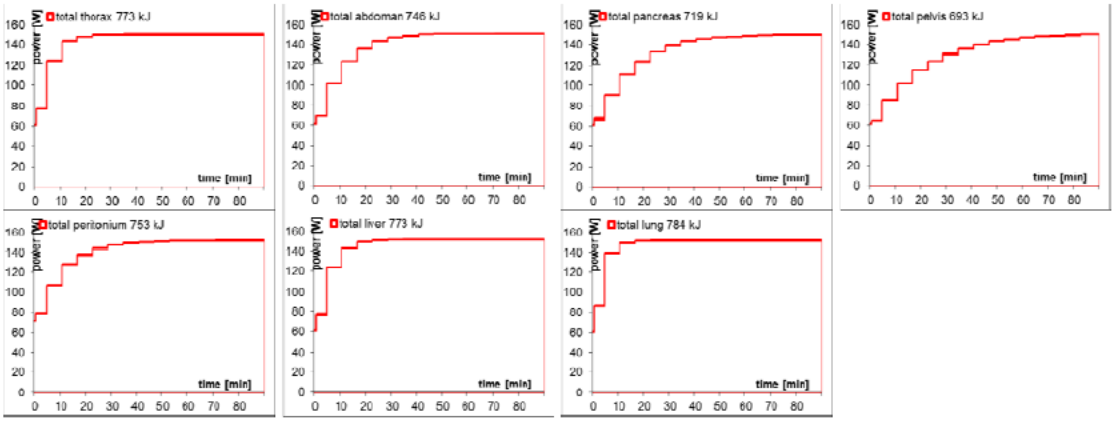
- ✓ Temperature measurement is not necessary, the energy control is valid
- ✓ We get the highest available RF-current, which does the decisional effect
- ✓ Oncothermia is extraordinarily safe and effective
- ✓ It is possible to make special protocol proposals for general use, and it modified by patients needs

Standard electrode (Ø20cm)

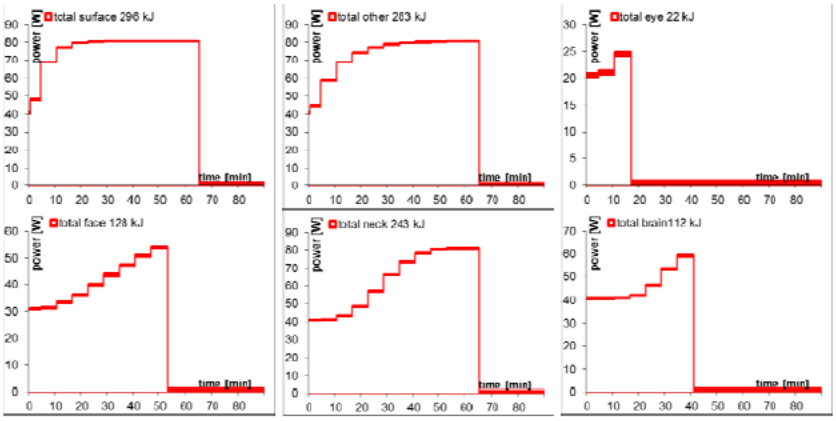




Large electrode (Ø30cm)



Small electrode (Ø10cm)



Conclusion

Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes possible the accurate and personalized treatment by this method.

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