Efficacy and dose of local hyperthermia

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Hyperthermia in oncology is based on energy-absorption from electromagnetic or mechanical sources. The specific absorption rate (SAR) measures the absorbed power (W/kg), and its multiplication by the duration of application in seconds gives the absorbed energy (J/kg). The dose is directly the absorbed energy, but in most of the applications, it is not a measurable parameter, due to the low efficacy of the absorption. The efficacy depends on the technical solution of the coupling of energy-source to the target, the surface cooling, and energy losses by the transmission, including the reflected power. The temperature is a consequence of the energy-absorption, and it depends on the thermal homeostatic activity of the targeted tissue.
Consequently, the inaccuracy of the SAR is mostly a technical problem, while the inaccuracy of the temperature is mainly physiological. The SAR is the source of the desired changes in the target, so it must be measured or at least estimated for dosing the local hyperthermia. The measured temperature is only an orienting parameter about the absorbed energy, and from that, we may calculate the SAR when otherwise it is not measurable. The planning is more straightforward; the SAR calculation with planning is a direct task, it is not necessary to transform it to the temperature of the target. This way the clue of dosing of local hyperthermia is the efficacy of the energy-targeting, making it possible to measure the applied dose with eligible accuracy. This approach needs well designed and controlled coupling for energy transfer to the tissue. My objective is to discuss the conditions of this request

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Efficacy and dose of local hyperthermia

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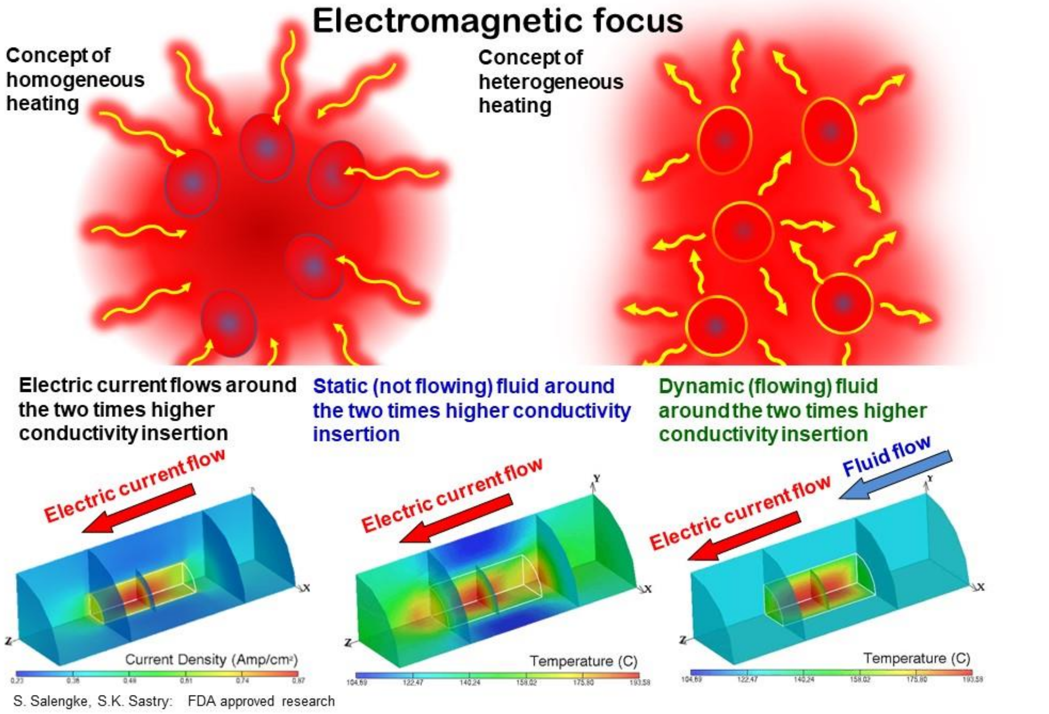
MOMENTUM OF INNOVATION

Outline

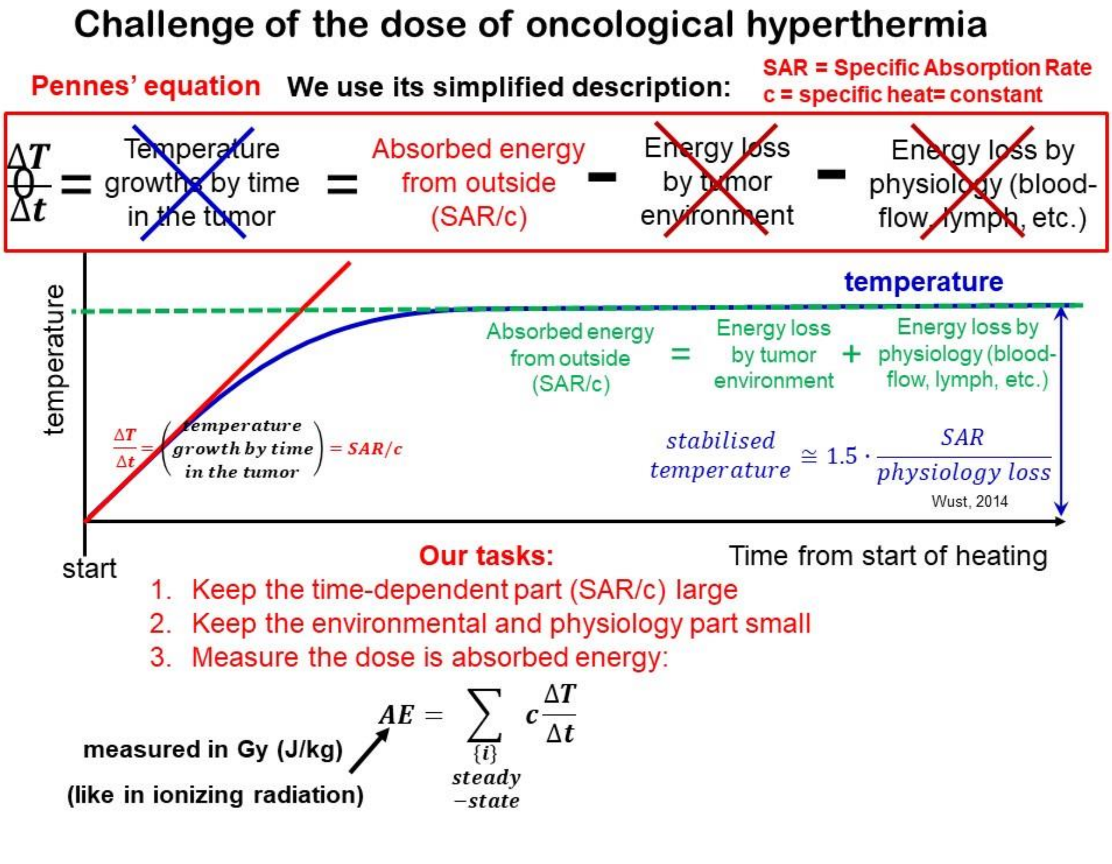
Our goal:

show a connection between the efficacy of the treating device and the measured dose vs measured temperature

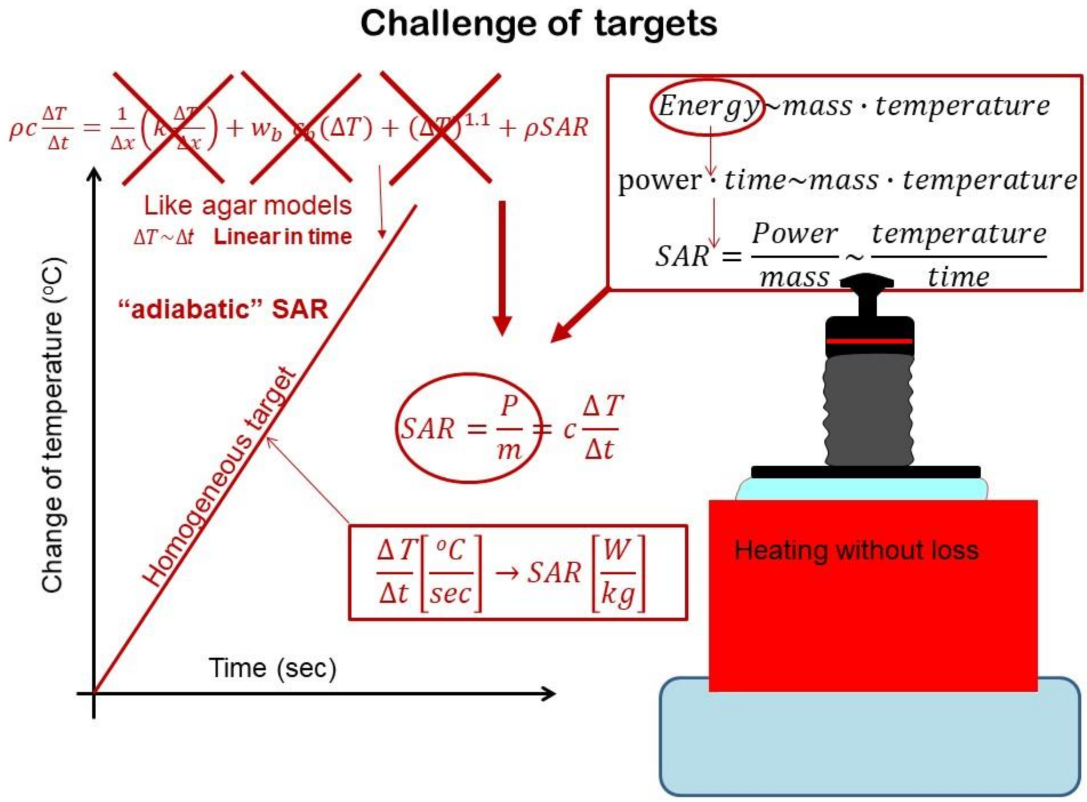
- The heating problem of heterogenic tumors
- The heating efficacy of hyperthermia
- The dose of hyperthermia
- Take-home message



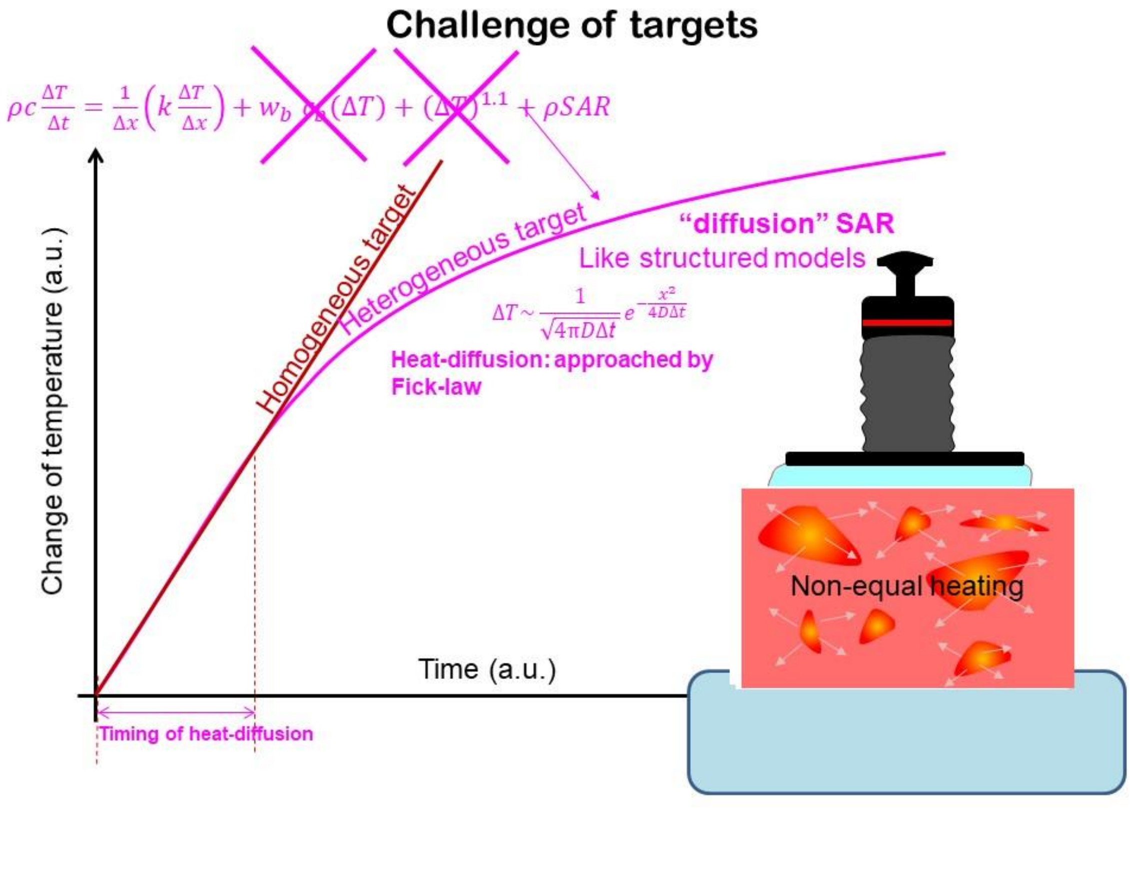
Electromagnetic focus
Concept of homogeneous heating
Concept of heterogeneous heating
Electric current flows around the two times higher conductivity insertion
Static (not flowing) fluid around the two times higher conductivity insertion
Dynamic (flowing) fluid around the two times higher conductivity insertion
Electric current flow
Electric current flow
Electric current flow
Fluid flow
Current Density (Amp/cm²)
Temperature (C)
Temperature (C)
S. Salengke, S.K. Sastry: FDA approved research



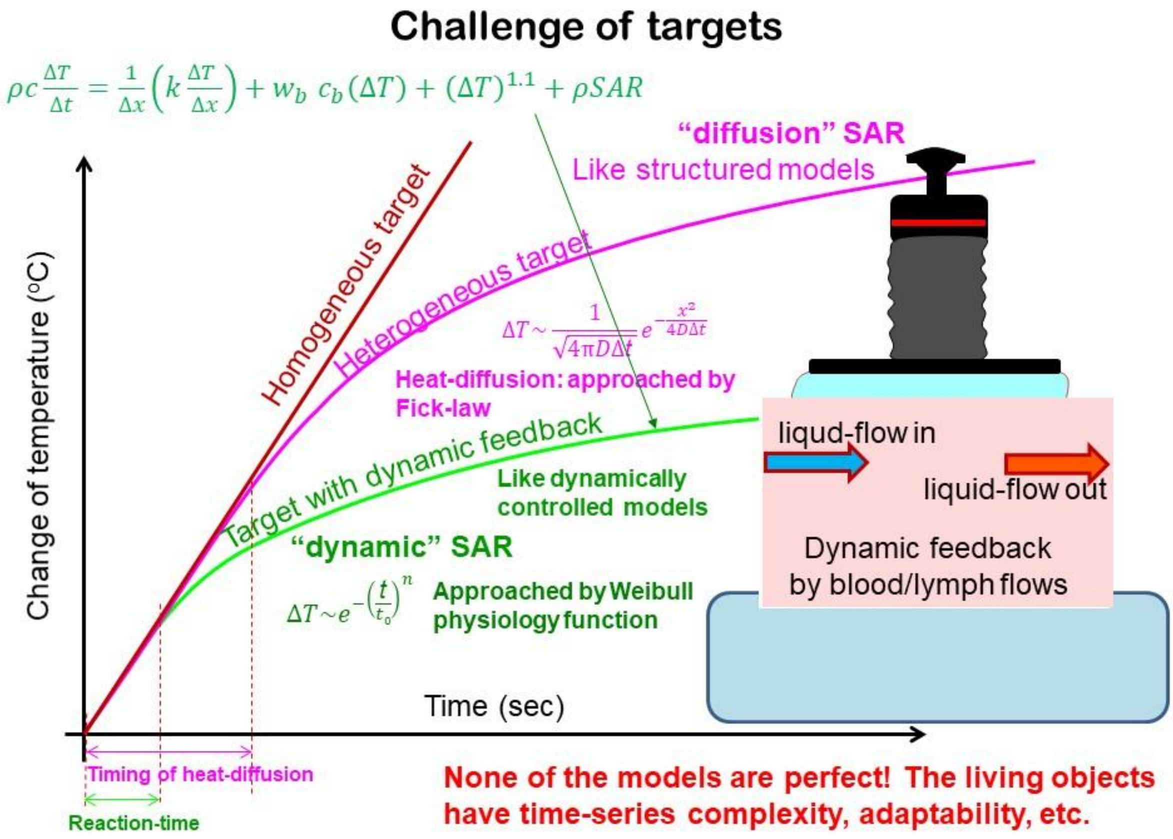
Challenge of the dose of oncological hyperthermia
Pennes' equation
We use its simplified description:
SAR = Specific Absorption Rate
c = specific heat= constant
$\frac{\Delta T}{\Delta t}$ = Temperature growths by time in the tumor = Absorbed energy from outside (SAR/c) - Energy loss by tumor environment - Energy loss by physiology (blood-flow, lymph, etc.)
temperature
temperature
Absorbed energy from outside (SAR/c) = Energy loss by tumor environment + Energy loss by physiology (blood-flow, lymph, etc.)
$\frac{\Delta T}{\Delta t} = \begin{pmatrix} temperature \\ growth\ by\ time \\ in\ the\ tumor \end{pmatrix} = SAR/c$
$\begin{matrix} stabilised \\ temperature \end{matrix} \cong 1.5 \cdot \frac{SAR}{physiology\ loss}$
Wust, 2014
start
Time from start of heating
Our tasks:
1. Keep the time-dependent part (SAR/c) large
2. Keep the environmental and physiology part small
3. Measure the dose is absorbed energy:
$AE = \sum_{\substack{\{i\} \\ steady \\ -state}} c\frac{\Delta T}{\Delta t}$
measured in Gy (J/kg)
(like in ionizing radiation)

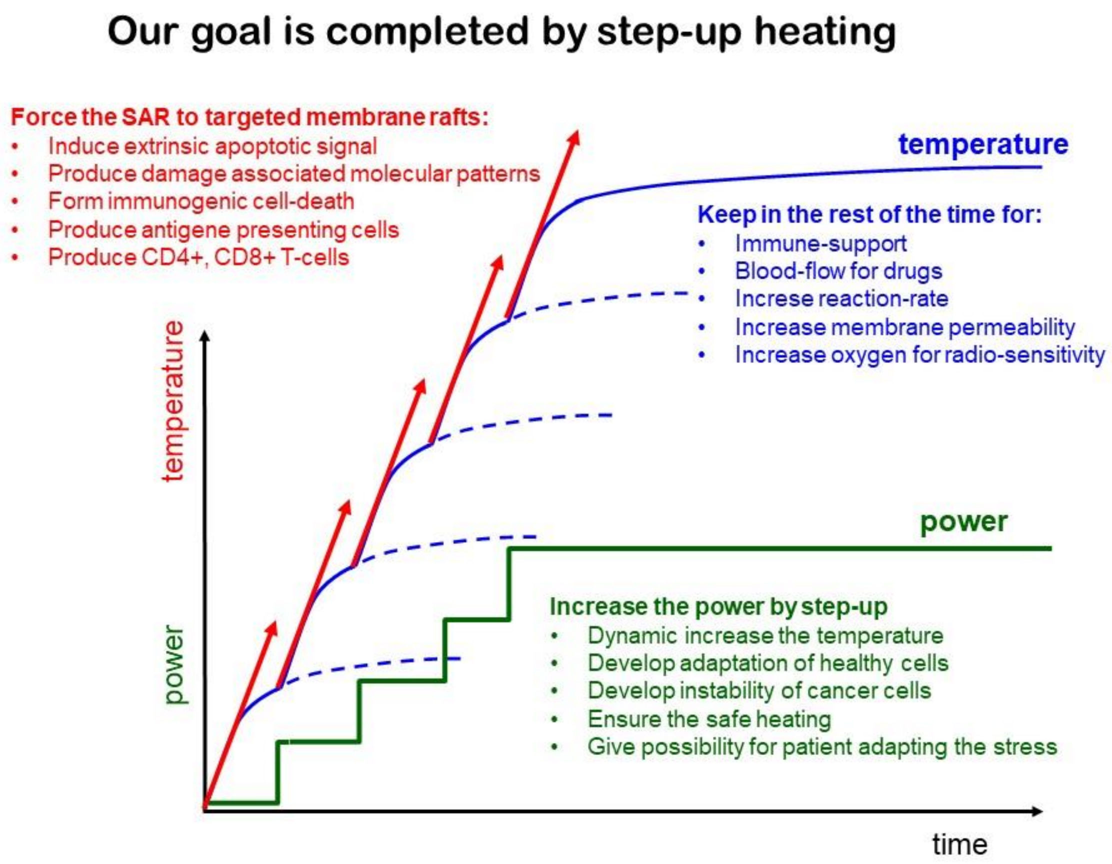


Challenge of targets
Energy~mass · temperature
power · time~mass · temperature
SAR = Power/mass ~ temperature/time
Like agar models
ΔT~Δt Linear in time
"adiabatic" SAR
Homogeneous target
SAR = P/m = c ΔT/Δt
ΔT/Δt [°C/sec] → SAR [W/kg]
Change of temperature (°C)
Time (sec)
Heating without loss



Challenge of targets
Homogeneous target
Heterogeneous target
"diffusion" SAR
Like structured models
Heat-diffusion: approached by Fick-law
Change of temperature (a.u.)
Time (a.u.)
Timing of heat-diffusion
Non-equal heating

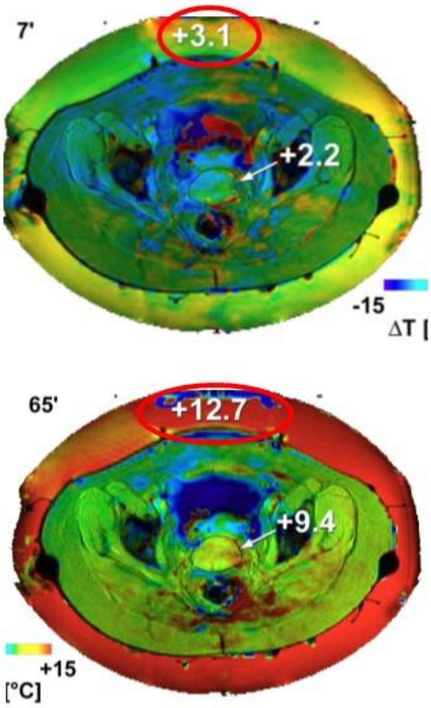

Challenge of targets
$\rho c\frac{\Delta T}{\Delta t} = \frac{1}{\Delta x}\left(k\frac{\Delta T}{\Delta x}\right) + w_b\, c_b(\Delta T) + (\Delta T)^{1.1} + \rho SAR$
"diffusion" SAR
Like structured models
Homogeneous target
Heterogeneous target
$\Delta T \sim \frac{1}{\sqrt{4\pi D\Delta t}}e^{-\frac{x^2}{4D\Delta t}}$
Heat-diffusion: approached by Fick-law
Target with dynamic feedback
Like dynamically controlled models
"dynamic" SAR
$\Delta T \sim e^{-\left(\frac{t}{t_0}\right)^n}$
Approached by Weibull physiology function
liqud-flow in
liquid-flow out
Dynamic feedback by blood/lymph flows
Change of temperature (°C)
Time (sec)
Timing of heat-diffusion
Reaction-time
None of the models are perfect! The living objects have time-series complexity, adaptability, etc.


Our goal is completed by step-up heating
Force the SAR to targeted membrane rafts:
• Induce extrinsic apoptotic signal
• Produce damage associated molecular patterns
• Form immunogenic cell-death
• Produce antigene presenting cells
• Produce CD4+, CD8+ T-cells
temperature
Keep in the rest of the time for:
• Immune-support
• Blood-flow for drugs
• Increse reaction-rate
• Increase membrane permeability
• Increase oxygen for radio-sensitivity
power
Increase the power by step-up
• Dynamic increase the temperature
• Develop adaptation of healthy cells
• Develop instability of cancer cells
• Ensure the safe heating
• Give possibility for patient adapting the stress
temperature
power
time

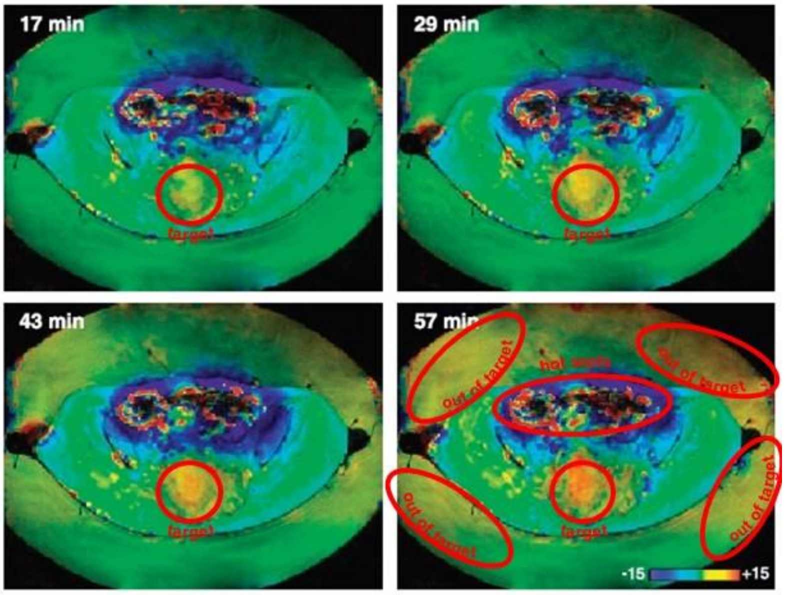
Outline

- ☑ The heating problem of heterogenic tumors
- ☐ The heating efficacy of hyperthermia
- ☐ The dose of hyperthermia
- ☐ Take-home message

Heterogeneity in large scale



RECENT ADVANCES IN TECHNOLOGY AND TECHNIQUE OF RF HYPERTHERMIA, Wlodarczyk W. Wust P, Seebass M, Gellermann J, Nadobny J. (Charite University Clinic, Berlin)

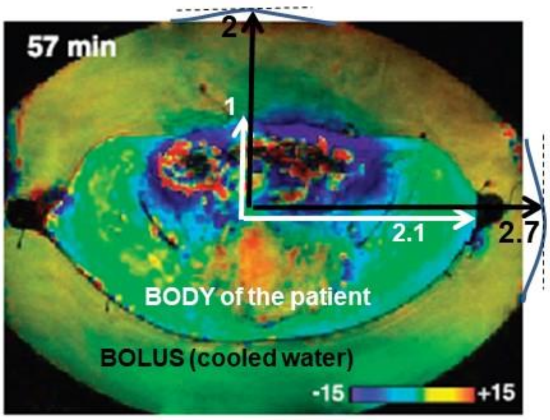


Gellermann J et al. Cancer Res 2005;65:5872-5880

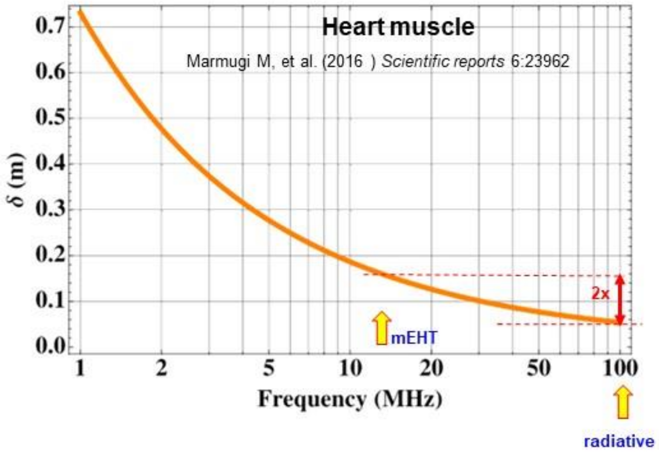
The water-bolus is heated more than the tumor.
It looks like a hot-bath.

How much energy is absorbed in the tumor?

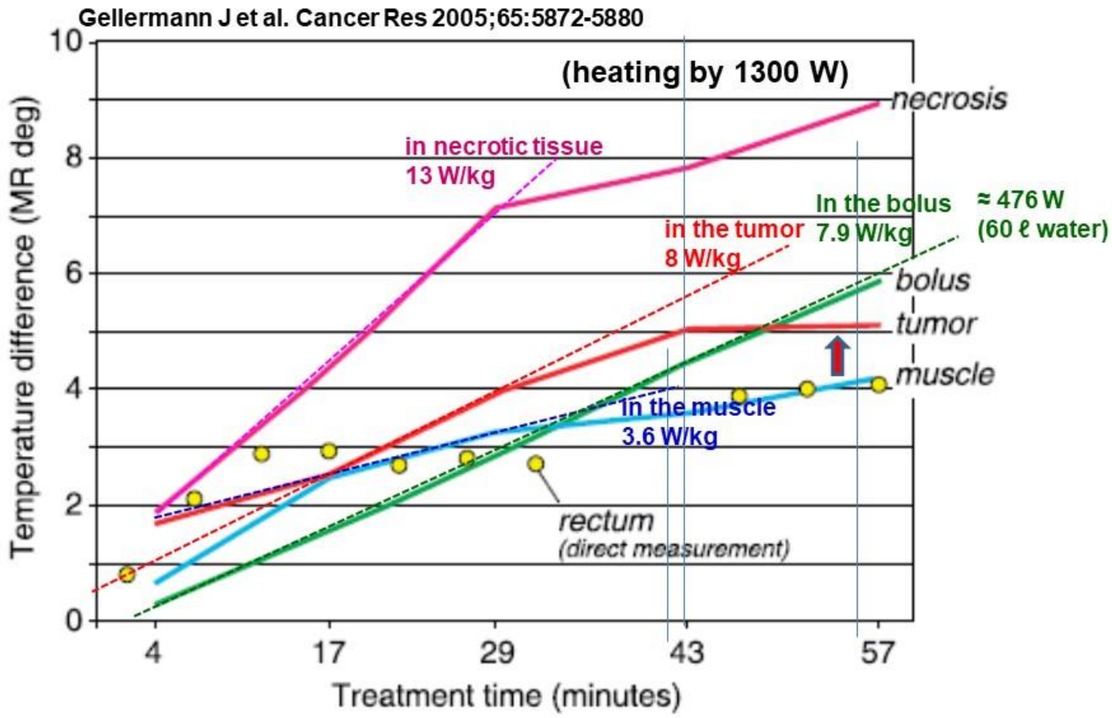
Gellermann, J. et al. (2005) *Cancer Research* 65:5872-5880.



Volume of the bolus is larger than the volume of the body-part by **157%**



How much energy is absorbed in the tumor?



Factors of energy losses

- **Radiation into the air (shielding is necessary)**
- **Cooling of the surface by large amount of water**
- **The thick bolus absorbes most of the energy**
- **The impedances for the proper surface match takes out energy**

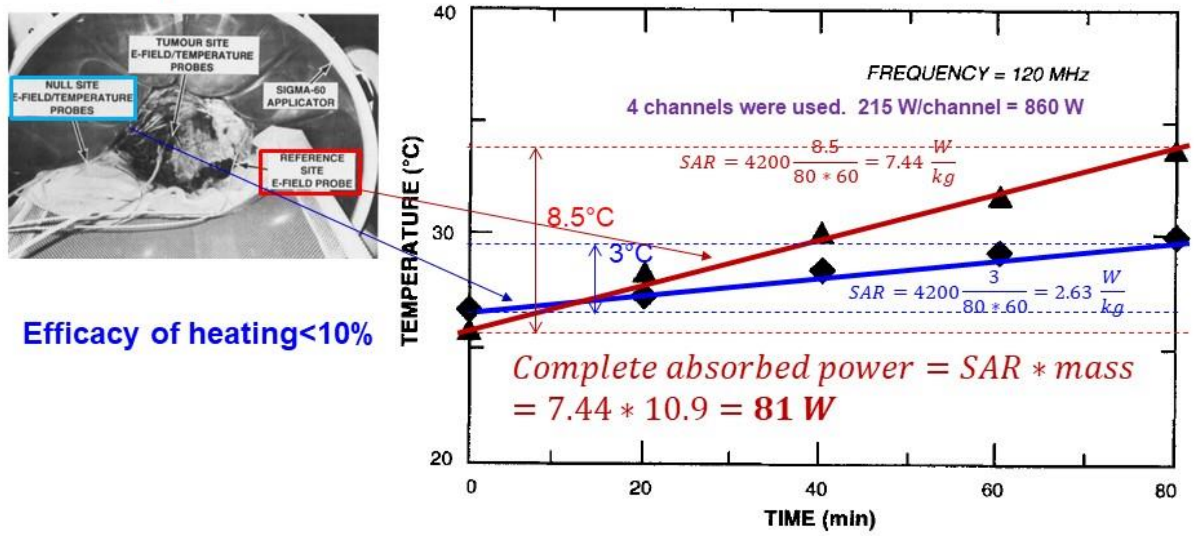
Consequences

1. The energy can not be used like it is in the case of ionizing radiation
2. The **efficacy** of the energy-absorption (**eliminate the losses**) must be drastically increased to use the absorbed energy as dose

Energy loss: Serious technical challenge

Temperature measurement in a phantom

Fenn AJ. King GA. Adaptive radiofrequency hyperthermia-phased array system for improved cancer therapy: phantom target measurements. Int. J. Hyperthermia. 10:189-208 (1994)

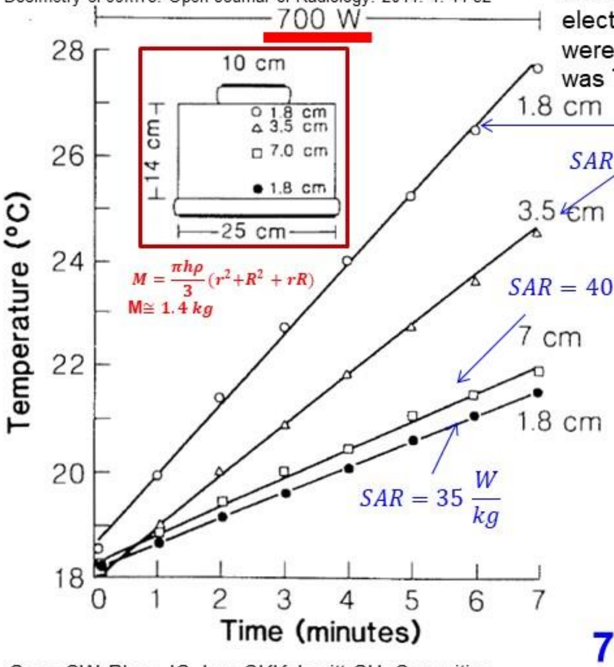


Here the measurement of the **temperature** is the **only way to approximate** the absorbed energy

Energy loss measurement: Thermotron

Agar gel mass density is 0.999 ± 0.004 kg/liter
Liliana Aranda-Lara. Eugenio Torres-García. Rigoberto Oros-Pantoja. Biological Tissue Modeling with Agar Gel Phantom for Radiation Dosimetry of 99mTc. Open Journal of Radiology. 2014. 4. 44-52

The changes in temperature at varying depths along the central axis of cylindrical agar phantom of 25 cm diameter and 14 cm thick. The phantom was heated with a pair of electrodes of 25 cm and 10 cm diameters. The electrodes were cooled with 20°C saline bolus and the power applied was 700 W.



$$SAR = 4200\frac{9}{7*60} = 90\ \frac{W}{kg}$$

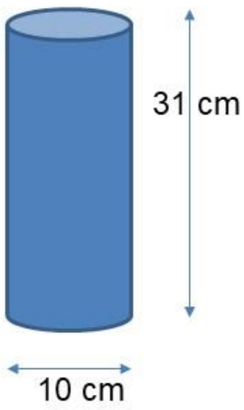
$$SAR_{average} = 70\ \frac{W}{kg}$$

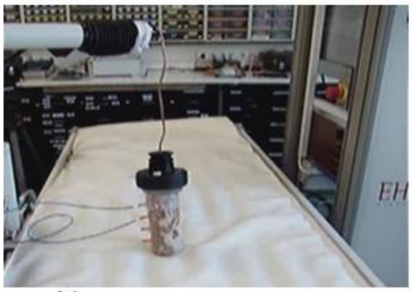
$$Complete\ power = SAR * mass = 70 * 1.4 = 98\ W$$

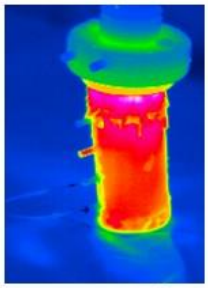
Song CW. Rhee JG. Lee CKK. Levitt SH. Capacitive heating of phantom and human tumors with an 8 MHz radiofrequency applicator (Thermotron rf-8) Int. J. Radiation Oncology Biol. Phys . 12:365-372

700 W was used, efficacy is 14%

Energy loss of oncotherm: chopped meat phantom





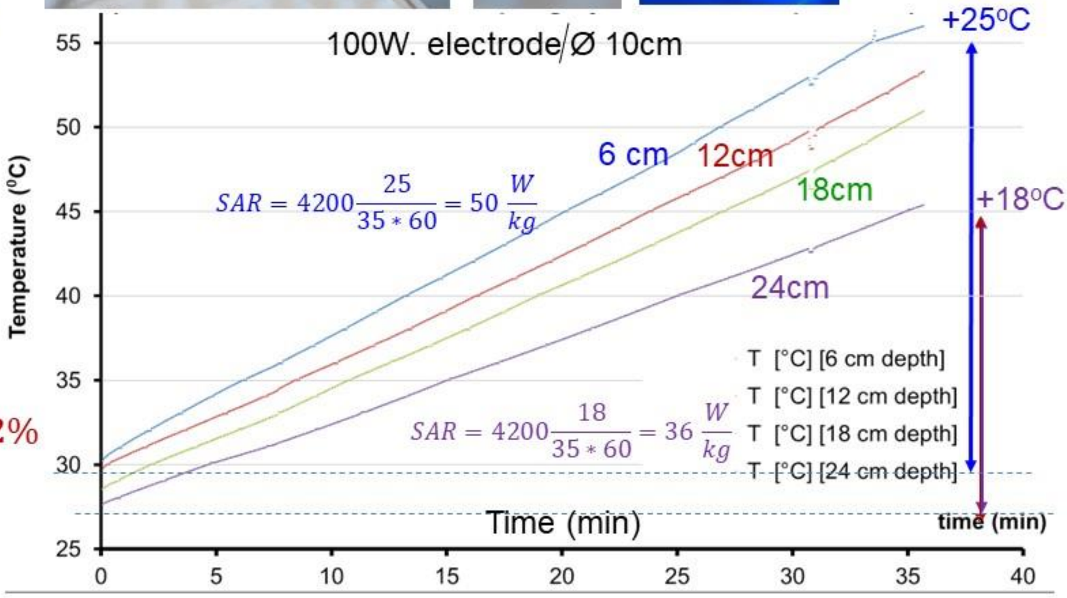


Nagy G. Meggyeshazi N. Szasz O (2013) Deep temperature measurements in oncothermia processes. Hindawi ;Conference Papers in Medicine. Volume 2013. Article ID 685264

Mass of meat $= 2.3\ kg$

Mean-energy $= 2.3\ kg * 40\frac{W}{kg} = 92W$

Efficacy = 92%



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The energy dose in clinical applications

Clinically we have to destroy the tumor, kill the tumor-cells.

With high, overall homogeneous heating (high CEM43ºCT$_{100}$) the goal is necrosis.

This kills the tumor-cells locally and the tumor vanishes when the temperature is high enough.

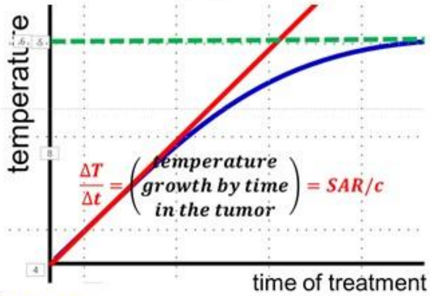
The only local elimination of malignancy gives good local control, however the malignancy is systemic.

Special apoptotic process (immunogenic cell-death, ICD) gives possibility to show the genetic information for immune-cells unhurt and train the system to fight all over the body, systemically.

The overall homogeneous heating is not selective, we need dynamic energy absorption instead of the static keeping of the temperature

To maintain the ICD the highly effective selective excitation of apoptotic signal pathways is necessary.

For control we must reduce the energy loss to available minimum, being sure, that the energy measures the real absorption in the target.



In case when the energy is mostly in the target, the dose is the provided energy.
SA (specific absorption) is defined in the standards, and it is the dose of heating

$$SA = \sum_N SAR(\tau)d\tau$$

SA is a sum of the SAR provided in the sessions and summed to all sessions

measured in Gy (J/kg) (like in ionizing radiation)

When the energy losses are considerable (the **efficacy of the heating device is low**) the **temperature measurement is mandatory** to control the only information about the energy absorption in the target.

The energy dose by SAR fits to clinical data

Francena M, et al. Eur. J. Cancer, 45:1969-1978 (2009)

Custom made thermal dose parameter based on T_{50} and duration of heating

$$TRISE = \frac{1}{5 \times 90} \sum_{n=1}^{n=max.} (T_{50} - 37^oC) \times dt$$

In mathematically correct form:

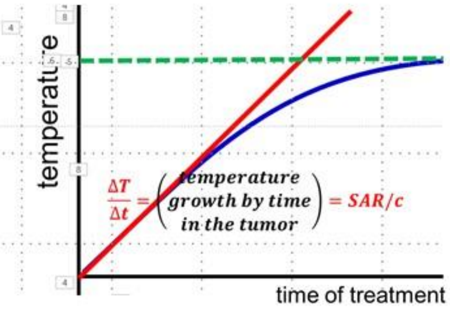
$$T_{rise} = n \sum_{time} \frac{[T_{50}(t) - 37^oC]}{t_s} \Delta t$$

number of sessions

duration of session

The principle is similar to the correct (SAR-based) dose, the temperature rise in time interval.

The value of $\frac{[T_{50}(t) - 37^oC]}{t_s}$ in careful step-up heating is a rough average of SAR,



in fact SAR fits to clinical data

$$T_{rise} \propto \sum_{N} SAR(\tau)d\tau$$

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Take home messages

My conclusion	My proposal
The heterogeneity of the heated tumor has special requests	Use careful step-up heating to optimize the energy-absorption in the target
Apply technique with highly efficient energy-absorption facility	The precise impedance matching allows to use the dose measured in J/kg (Gy)
Use proper selection to direct the energy on the target	Use biophysical differences to target the cancer cells
The deep targeted heating is a complex task, has to be combined with electric field	The effects of electric field on the cellular damage have to be considered
The temperature is a condition of the optimizing of the effects	The temperature must be below the necrotic level
When the heating efficacy is small the temperature must be measured to have idea about the absorbed energy	Increase the heating preciosity for not necessity the temperature measurement

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Thank you very much for your attention

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