Challenges and proposals in local oncological hyperthermia

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Challenges and proposals in local oncological hyperthermia

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Introduction

Local hyperthermia in oncology has numerous challenges which must be solved for further development of this excellent method. We have to clearly recognize what are the drawbacks and find the way to eliminate them using the latest technical and medical knowledge. Application of hyperthermia apparently looks (but only looks!) very simple, so various "household" or technically underdeveloped solutions are applied widely, which tends to charlatanism and has a danger about the complete negative opinion from the medical experts.

Methods

There are multiple approaches to heat up the tumor homogeneously as much as possible satisfying the necrotic cell-killing, how CEM43 dose definition requests it. This dose has some basic problems: (1) scientifically the formal fit to the data of the measurements is incorrect by its dimensionality due to the difference of the temperature is used without its actual physical dimension, (2) technically it requests solving the deep selective heating with its proper temperature control; (4) further technical challenge is the proper measurement of the heating homogeneity of the anyway heterogenic tumor; (3) experimentally it is based on necrosis (in vitro reference) which is far away from the medical reality; (4) medically it does not consider the physiological data (blood-flow, invasion, dissemination, non-necrotic cellular changes, etc. The proper dose definition is a crucial request build acceptance of the oncological hyperthermia worldwide [1].

Results

The attempts by artificial focusing of the electromagnetic waves have partial solution considering only the properly heated portion of the tumor (Tx percent of CEM43Tx). Furthermore, escaping from the medical encounter, only local control is chosen like the endpoints of the trials or only locally advanced tumors (metastases do not exist) are included in the trial protocols. This limits the applicability of oncological hyperthermia to the less life-threatening stages, while its application is usually applied after when the low-line conventional treatments offer unsatisfactory results. Additional drawback of hyperthermia is the rapid development of non-hyperthermia therapies, like the targeted therapies, personalized therapies and immune-oncology. Our primary task is to avoid the declining prestige of oncologic hyperthermia. As a result of the direct facing of the problems we have to answer to special questions:

1. What is the optimal deep hyperthermic temperature and how homogeneously does it have to be provided?

2. How to solve the selection between the healthy and cancerous cells, keeping the heathy cells unharmed, when recognizing the emphasized heterogeneity of the tumor?
3. What is the dose which is accurate, reproducible and safe to control an optimal treatment?
4. How the systemic malignancy (micro and macrometastases) could be blocked by local action of heating?

There are numerous solutions proposed [2], [3], [4].

Conclusion

Answers to the above questions and solutions for the challenges exist [5]. We have to conclude that our task is to reestablish the prestige of oncological hyperthermia that had shown so many good results as well as had produced multiple disappointing controversies until now.

References

1 Jones, E., et al. (2006) Prospective Thermal Dosimetry: The Key to Hyperthermia's Future. Int. J. of Hyperth., 22:247-253

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INTRODUCTION

Local hyperthermia in oncology has numerous challenges which must be solved for further development of this excellent method. We have to clearly recognize what are the drawbacks and find the way to eliminate them using the latest technical and medical knowledge. Application of hyperthermia apparently looks (but only looks!) very simple, so various "household" or technically underdeveloped solutions are applied widely, which tend to charlatanism and has a danger about the complete negative opinion from the medical experts.

General challenge: how to raise the prestige of hyperthermia again to the top of oncotherapies, as it was at its start?

❶ **Challenge of definition of oncological hyperthermia**: no clear definition of oncological hyperthermia is declared

Present convention
Oncology encyclopaedia – hyperthermia is ***therapeutic heat***
Medicine.net – overheating of the ***body***
National Cancer Institute – body ***tissue*** is exposed to high temperatures (***up to 45°C***)
Wikipedia – body ***tissue*** is exposed to ***slightly higher*** temperatures to damage and ***kill*** cancer cells or to make cancer cells more ***sensitive*** to the effects of radiation and certain drugs
Medical Dictionary – ***much higher*** than normal body temperature induced therapeutically or iatrogenically
The Am. Canc. Soc. – ***body*** is exposed to ***higher than normal*** temperatures, changes take place inside the ***cells***

Oncothermia definition Oncological hyperthermia is a method to ***kill malignant cells by*** heat-inducing absorbed ***energy and/or sensitize*** certain complementary therapies

❷ **Challenge of safety of the radiation of hyperthermia** The safety needs low level electromagnetic radiation to keep the health standards, and make no disturbances on the nearby medical equipments.

Present conventions
1. using frequencies out of medical standards Complete shielding of the treatment room is necessary (huge extra cost and complications)
2. applying huge energy with low efficacy Not known how much is the absorbed energy at the radiative one, so we have to measure the temperature to have an idea about the absorbed energy, ensure the safety

Oncothermia solution
1. strict impedance coupling by application of the frequency according to the medical standards
2. application of high absorption efficacy (a) to reduce the radiation near the treatment-bed (b) to measure the absorbed energy without temperature control

❸ **Challenge by other therapies** New challenger therapies intensively developed recently by targeted therapies and immune-oncology; solving the above problems by the non-hyperthermic way.

Present complementary & competitive therapies
Surgery minimally invasive (robotic, endoscopic, laparoscopic, etc.)
Radiotherapy proton and heavy ion therapies, tomotherapy, radiative seed-therapies, etc.
Chemotherapy oral drugs, antibody therapies, immune-effects, check-point inhibitors, etc.
New diagnostics circulation tumor cells (CTC), free DNA, microRNA, proteomics, exosomes etc.
Theranostics a combination of diagnostics and therapy

Oncothermia solution for competence Local, selective heat-therapy directly targets the tumor-cells by their biophysical characters **It is a modern theranostics that detects the tumor and treats it**

❹ **Challenge of selection (focusing)** Selection of the malignant parts in the targeted volume (focusing)

Present convention Focusing the electromagnetic waves, similarly to ionizing radiation
1. The **dipole antenna** wave needs high frequency for focusing, where the penetration depth rapidly decreases, most of the energy is absorbed by the coupling bolus, lost control on the absorbed energy.
2. In **plane-wave** the focus is roughly approximated by the size of electrodes. The rough size variation loses the control on the real absorbed energy in the targeted tumor.

Oncothermia solution Select cellularly by the biophysical differences of malignant cells from their healthy counterparts. The RF-current actively selects the malignancy on cellular level.

❺ **Challenge of the dose of oncological hyperthermia**

Present conventions $CEM43^{\circ}CT_x$ Calibrated in vitro Sapareto and Dewey, THERMAL DOSE DETERMINATION IN CANCER THERAPY Int.J.Rad. Onc.ol. Biol. Phys., 10:787-800

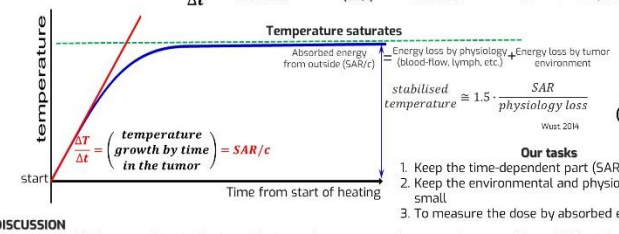
$$CEM43^{0}C = \sum_{\substack{\{i\}\\ steady\\ -state}} t_i R^{(T_C - T_i)} \qquad T_c = 43^{\circ}C \qquad R = \begin{cases} 0.25 & T < 43^{\circ}C \\ 0.5 & T \geq 43^{\circ}C \end{cases}$$

a. scientifically incorrect: $R^{(T-43^{\circ}C)}$ has no unit
b. thermal **necrosis** concept
c. calibrated **in vitro**
d. estimation of **heterogeneities** (T_x)
e. Arrhenius kink depends on chemotherapies
f. Eyring reaction-kinetics is not used

T_{RISE} Fit to the clinical data Francenia M, et al. Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur. J. Cancer, 45:1969-1978 (2009)

$$T_{RISE} = \sum_{\substack{\{i\}\\ steady\\ -state}} t_i \frac{(T_{50} - 37^{\circ}C)}{treat.time}$$ Rough average in time and space (unprecise, incorrect)

Oncothermia solution $\frac{\Delta T}{\Delta t}$ = 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.) (Pennes' equation)
SAR = Specific Absorption Rate
c = specific heat- constant



Our tasks
1. Keep the time-dependent part (SAR/c) large
2. Keep the environmental and physiology part small
3. To measure the dose by absorbed energy

The correct dose

$$AE = \sum_{\substack{\{i\}\\ steady\\ -state}} \frac{1}{c}\frac{\Delta T}{\Delta t} = \sum_{\substack{\{i\}\\ steady\\ -state}} SAR = \sum_{\substack{\{i\}\\ steady\\ -state}} \frac{t_i \cdot Power\ (W)}{heated - mass}$$

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

DISCUSSION

There are multiple approaches to heat up the tumor homogeneously as much as possible satisfying the necrotic cell-killing, how CEM43 dose definition requests it. This dose has some basic problems: (1) scientifically the formal fit to the data of the measurements is incorrect by its dimensionality due to the difference of the temperature is used without its actual physical dimension, (2) technically it requests solving the deep selective heating with its proper temperature control; (4) further technical challenge is the proper measurement of the heating homogeneity of the anyway heterogenic tumor; (3) experimentally it is based on necrosis (in vitro reference) which is far away from the medical reality; (4) medically it does not consider the physiological data (blood-flow, invasion, dissemination, non-necrotic cellular changes, etc. The proper dose definition is a crucial request to have acceptance of the oncological hyperthermia worldwide [1].
The attempts by artificial focusing of the electromagnetic waves have partial solution considering only the properly heated portion of the tumor (Tx percent of CEM43Tx). Furthermore, escaping from the medical encounter, only local control is chosen like the endpoints of the trials or only locally advanced tumors (metastases do not exist) are included in the trial protocols. This limits the applicability of oncological hyperthermia to the less life-threatening stages, while its application is usually applied after when the low-line conventional treatments offer unsatisfactory results. Additional drawback of hyperthermia is the rapid development of non-hyperthermia therapies, like the targeted therapies, personalized therapies and immune-oncology. Our primary task is to avoid the declining prestige of oncologic hyperthermia. As a result of the direct facing of the problems we have to answer to special questions:
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CONCLUSION

Temperature measurement is necessary in conventional hyperthermia having idea about the absorbed energy in the tumor-mass

Answers to the above questions and solutions for the challenges exist [5]. We have to conclude that our task is to reestablish the prestige of oncological hyperthermia that had shown so many good results as well as had produced multiple disappointing controversies until now.

For oncothermia:

The absorbed energy is the dose. Its unit is the kGy=J/g
❶ Don't be isothermal (no homogeneous heating)
❷ Heat the malignant cells selectively
❸ Use high heating efficacy, less energy-loss
Use adaptive treatment protocol instead of planning
❶ regulate the process by actual site and stage of the disease
❷ expand the local treatment to systemic (immune effects)
❸ be adaptive for patients' complaints