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 healthy 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**

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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 brings (but only limited) very small, so various "household" or technically undervaluated benefits, which lead to utilization and has changed: 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?

1. Challenge of definition of oncological hyperthermia: no clear definition of oncological hyperthermia is declared

Present convention: Oncology encyclopedia - Hyperthermia is in therapeutic heat
Modern heat - overheating of the body
National Cancer Institute - body is exposed to high temperatures (up to 43°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 surgically

The Amer. Canc. Soc. - body is exposed to higher than normal temperatures, changes take place inside the cells

2. Challenge of safety of the radiation of hyperthermia: the safety needs low level electromagnetic radiation toward the health standards, and make no disturbances on the nearby medical equipments.

Present conventions:
1. using frequencies out of medical standards
2. relying huge energy with low efficiency
3. Not known how much is the absorbed energy at the indicated one, so we have to measure the temperature to have an idea about the absorbed energy
Oncothermia solution: 1. select frequencies below heating of the frequencies according to the medical standards
2. application of High absorption efficiency (α) to reduce the dose toward the treatment-bed (t) to measure the absorbed energy without temperature measurement

3. Challenge by other therapies: new challenges therapies, intensively developed recently by targeted therapies, immune-oncology solving the above problems by the non-Hyperthermic way

Present complementary & competitive therapies:
Surgery: minimally invasive (laparoscopy, endoscopy, bronchoscopy, etc.)
Radiotherapy: proton and heavy ion therapies, tomotherapy, catheter-based seed therapies, etc.
Chemotherapy: oral, drugs, antibody therapies, immune-effects, check point inhibitors, etc.
New diagnostics: circulation tumor markers (CTC), free DNA, microRNA, proteomics, xenomes, etc.
Theranostics: a combination of diagnostics and therapies

Oncothermia solution for competition: Local, selective heat therapy directly targets the tumor-cells by their biological characters. It is a modern theranostics that detects the tumor and treats it

4. Challenge of selection (focusing): the selection of the malignant parts in the volume (focusing)

Present convention: Focusing the electromagnetic waves, similarly to ionizing radiation
1. the epiderm tissue wave needs high frequency for focusing, where the penetration depth rapidly decreases, most of the energy is absorbed by the coupling buffer, less 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 absorbed energy in the targeted tumor

Oncothermia solution: Select calorically by the biophysical differences of malignant cells from their healthy counterparts. The R-F current-activity select the malignant on cellular level.

5. Challenge of the dose of oncological hyperthermia

Present convention: CEWA57°C, Calculated in U.S. Army Medical Research & Material Command, Attn: Medical Equipment Division, Medical Radioisotope, and Hyperthermia, June 2021

\[ C \times E \times A \times 5 = \frac{E \times A \times 5}{C} \]

Where: E = Energy, A = Absorbed amount, 5 = Five minutes, C = Cooling factor

Oncothermia solution: Fit to the clinical data

\[ T_{1/2} = \frac{T_{0} - 37°C}{2} \]

T1/2 = Time to half of the initial temperature

T0 = Initial temperature

The correct dose

\[ AE = \frac{1}{c} \times \frac{1}{\Delta T} \times 1 \]

AE = Amount of energy, c = Cancer cell, ΔT = Temperature change

REFERENCES


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