ONCOTHERMIA JOURNAL

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Editorial

Dear Readers, Dear Fellow Researchers, Dear Colleagues, Dear Friends,

The recent volume of the Oncothermia Journal is the 27th now. We had started this open-access publication in 2011 intending to give information for Oncothermia users and interested specialists about the actual professional news and results in clinical and experimental topics. I am pleased to recognize the wide interest of the actual publications and see how the OJ started to be a reference source for many experts.

The present volume shows a representing material from the 37th annual conference of International Clinical Hyperthermia Society held in Thessaloniki, Greece. The two-days event was a great success having intensive discussions about the actual research challenges and possible solutions. Most of the presentations were centred on clinical results that showed excellent statistical pieces of evidence on relapsed glioblastoma multiform cases as well as the possibility of induced immunogenic effects by modulated electro-hyperthermia (mEHT) to cure this serious disease. The immunotherapy combination with mEHT was presented not only in gliomas, but in ovarian cancer too. The advanced pancreatic cancer, which has poor survival in conventional treatments, was discussed and significant improvements were revealed in the survival of this aggressive disease.

These presentations are completed with some theoretical considerations on methodology and clinical practice. I do hope that the present volume offers numerous new information, proving the strong developments of the complex hyperthermia technologies. I recommend this volume for everyone who are eager to know more about the present status of this emerging therapy option.

I hope this information offers you additional opportunities to help your suffering patients.

Sincerely yours,
Prof. Dr. Andras Szasz

Liebe Leserinnen und Leser, liebe Kolleginnen und Kollegen aus Forschung und Praxis,

Sie halten die mittlerweile 27. Ausgabe des Oncothermia Journals in Ihren Händen. Wir haben 2011 mit der Publikation dieses Open-Access-Journals begonnen um Informationen zur Oncothermie für Anwender und Spezialisten bereitzustellen und einen Einblick in Neuigkeiten und aktuelle Ergebnisse von klinischen und experimentellen Themen zu geben. Es freut mich sehr zu sehen, dass die gegenwärtige Publikation so großen Zuspruch erfährt und das Oncothermia Journal sich zu einer Referenzquelle für zahlreiche Experten entwickelt.

Der aktuelle Band stellt einige Inhalte der jährlich abgehaltenen 37. International Clinical Hyperthermia Society Konferenz in Thessaloniki, Griechenland, dar. Das zweitägige Event war ein voller Erfolg, mit intensiven Diskussionen über die derzeitigen Herausforderungen der Forschung sowie deren Bewältigung. Die meisten Vorträge legten den Fokus auf klinische Ergebnisse die statistisch belegte Beweise für Fälle von rezidivierten Glioblastoma Multiforme enthielten, sowie die Möglichkeit von immunogen induzierter Wirkung durch modulierte Elektro-Hyperthermie (mEHT), um diese schwerwiegende Krankheit zu heilen. Die Kombination von Immuntherapie mit mEHT wurde nicht nur im Zusammenhang mit Gliomen, sondern ebenfalls bezogen auf Ovarialkrebs dargelegt. Auch über fortgeschrittenen Bauchspeicheldrüsenkrebs, bei dem Betroffene nur geringe Überlebenschancen haben, wenn sie mit konventionellen Methoden behandelt werden, wurde diskutiert und es wurden signifikante Fortschritte für das Überleben dieser aggressiven Krankheit aufgezeigt.

Die vorliegenden Präsentationen wurden durch einige theoretische Betrachtungen im Bezug auf Methodik und klinische Praxis ergänzt. Ich hoffe inständig, dass die derzeitige Ausgabe zahlreiche neue Informationen enthält, welche die überzeugenden Entwicklungen der vielschichtigen Hyperthermie-Methode belegen. Empfehlen möchte ich dieses Journal allen, die mehr über den derzeitigen Stand dieser aufkommenden Therapiemöglichkeit wissen wollen.

Ich hoffe, die Inhalte dieses Journals bieten Ihnen zusätzliche Möglichkeiten, um Ihren leidenden Patienten zu helfen.

Mit freundlichen Grüßen,
Prof. Dr. Andras Szasz

Imprint

Rules for submission

As the editorial team we are committed to a firm and coherent editorial line and the highest possible printing standards. But it is mainly you, the author, who makes sure that the MEHT Journal is an interesting and diversified magazine. We want to thank every one of you who supports us in exchanging professional views and experiences. To help you and to make it easier for both of us, we prepared the following rules and guidelines for abstract submission.

Als redaktionelles Team vertreten wir eine stringente Linie und versuchen, unserer Publikation den höchst möglichen Standard zu verleihen. Es sind aber hauptsächlich Sie als Autor, der dafür Sorge trägt, dass das MEHT Journal zu einem interessanten und abwechslungsreichen Magazin wird. Wir möchten allen danken, die uns im Austausch professioneller Betrachtungen und Erfahrungen unterstützen. Um beiden Seiten die Arbeit zu erleichten, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope
The MEHT Journal is an official journal of the Oncotherm Group, devoted to supporting those, who would like to publish their results for general use. Additionally, it provides a collection of different publications and results. The MEHT Journal has an open-minded character, but it should particularly contain complete study-papers, case-reports, reviews, hypotheses, opinions, and all the informative materials which could be helpful for the international Oncotherm community. Advertisement connected to the topic is also welcome.

- Clinical Studies: Regional or local or multilocal mEHT or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, MEHT in combination with other modalities, and treatment optimization.
- Biological Studies: Mechanisms of mEHT, thermal-or non-temperature dependent effects, response to electric fields, bioelectromagnetic applications for tumors, MEHT treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- Techniques of mEHT: Technical development, new technical solutions, proposals.
- Hypotheses, suggestions, opinions to improve mEHT and electro-cancer-therapy methods, intending the development of the treatments.

Further information about the Journal, including links to the online sample copies and content pages can be found on the website of the journal: www.MEHT-Journal.com.

1. Selbstverständnis und Ziele
Das MEHT Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das MEHT Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncotherm-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- Klinische Studien, regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen.
- Biologische Studien. Mechanismen der Oncothermie, thermale oder temperaturunabhängige Effekte, Ansprechen auf elektrisches Feld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
- Oncothermie-Techniken. Technische Entwicklungen, neue technische Lösungen.
- Hypothesen, Meinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen.

2. Submission of Manuscripts
All submissions should be made online via email: MEHT-Journal@oncotherm.org.

2. Manuskripte einreichen
Manuskripte können online eingereicht werden: MEHT-journal@oncotherm.org

3. Preparation of Manuscripts
Manuscripts must be written in English, but other languages can be accepted for special reasons, if an English abstract is provided.

Texts should be submitted in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be submitted in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be provided in JPG format.

Manuscripts may be any length, but must include:

- Title Page. Title of the paper, authors and their affiliations, 1-5 keywords. At least one corresponding author should be listed, whose email address and full contact information must be provided.
- Abstracts. Abstracts should include the: purpose, materials, methods, results and conclusions.
- Test. Unlimited volume.
- Tables and Figures. Tables and figures should be referred to in the text (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without a reference to the text. Figure files will ideally be submitted as jpg-file (300dpi for photos).
- References. MEHT Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3], [1-3]. The full references should be listed numerically in order of appearance, and presented following the text of the manuscript.

3. Manuskripte vorbereiten
Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.

Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.

Manuskripte können jede Längen haben, müssen aber die folgenden Punkte enthalten:

- Titelseite. Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte. Es muss mindestens ein Autor ausgewiesen sein, dessen Email-Adresse und Kontaktdetails angegeben werden.
- Abstracts. Abstracts müssen enthalten: Zielsetzung, Material und Methoden, Ergebnisse, Fazit.
- Text. Beliebige Länge.
- Abbildungen und Tabellen. Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg verwendet werden (300 dpi).
- Zitate. Das MEHT Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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When the proofs are ready, the corresponding authors will receive an e-mail notification. Hard copies of proofs will not be mailed. To avoid delays in the publication, corrections to proofs must be returned within 48 hours, by electronic transmittal or fax.

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Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per Email informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhindern, müssen die korrigierten Texte innerhalb von 48 Stunden per Email oder Fax zurückgesandt werden.

6. Offprints and Reprints
Author(s) will have the opportunity to download the materials in electronic form and use it for their own purposes. Offprints or reprints of the MEHT Journal are not available.

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Die Autoren haben die Möglichkeit, das Material in elektronischer Form herunterzuladen, Sonderdrucke und Nachdrucke des MEHT Journals sind nicht erhältlich.

7. Advertising
The MEHT Journal accepts advertising in any language but prefers advertisements in English or at least partially in English. The advertising must have a connection to the topics in the MEHT Journal and must be legally correct, having checked that all information is true.

7. Werbung
Das MEHT Journal akzeptiert Werbeanzeigen in allen Sprachen, wünscht aber die zumindest teilweise Gestaltung in englischer Sprache. Die Werbung muss eine Beziehung zu den Themen des MEHT Journals haben und der Wahrheit entsprechende Inhalte aufweisen.

8. Legal responsibility
Authors of any publications in the MEHT Journal are fully responsible for the material which is published. The MEHT Journal has no responsibility for legal conflicts due to any publications. The editorial board has the right to reject any publication if its validity has not been verified enough or the board is not convinced by the authors.

8. Haftung
Die Autoren aller im MEHT Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das MEHT Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Der redaktionelle Beirat hat das Recht, Artikel abzulehnen.

9. Reviewing
The MEHT Journal has a special peer-reviewing process, represented by the editorial board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of the reviewer will not be released, and her/his name will be handled confidentially. Papers which are not connected to the topics of the journal could be rejected without reviewing.

9. Bewertung
Die Texte für das MEHT Journal werden vom redaktionellen Beirat kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden.

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Contents

Computational study of simplified numerical phantoms inside capacitive hyperthermia devices

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Presented at the 37th ICHS, Thessaloniki

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www.oncotherm.com/sites/oncotherm/files/2019-10/Computational_study_of_simplified.pdf

Introduction

Capacitive hyperthermia is often used in conjunction with radiotherapy and chemotherapy for the treatment of cancer. It is applied by the use of electrodes, which can be either changeable or fixed. The main frequencies used for this electromagnetic heating modality are 8 and 13.56 MHz. In order to achieve better coupling of the electromagnetic energy to the body and, at the same time, cool the surface tissues, all devices use a water bolus between the application electrode and the body, commonly with a cooled circulating liquid. However, not much work has been performed until now on the treatment planning with such devices [1, 2].

Objectives

The objective of the current study was to investigate the distributions of the electric field, the specific absorption rate (SAR) and the temperature inside a simplified numerical phantom of the human torso with an embedded spherical tumor, when the number, shape and positioning of electrodes were changed to achieve an optimized treatment. Finally, we also aimed at examining the effect of optimal positioning derived with the simplified model on a numerical phantom of realistic anatomy.

Material/Methods

The software platform we used for performing the numerical simulations was Sim4Life Version 4.4.2 (Zurich Med Tech, Zurich, Switzerland), which implements the Finite Element Method (FEM). A homogenous numerical phantom of the torso (cylindrical with elliptical cross-section) was created. The phantom comprised two tissues: an internal cylinder with small and large diameters of 40 cm and 72 cm, respectively, which was assigned to the electric conductivity of muscle, and a cylindrical shell of 2 cm thickness on top, which was assigned to the properties of fat. The realistic model of 'Ella' from the Virtual Population (IT'IS Foundation, Zurich, Switzerland) was also used and studied; this model represents a 26-year-old female with the height of 1.63 m and 57 kg. The circular electrodes simulated were of 25 cm in diameter.

Results

It was confirmed that the number and size of the electrodes induce differences in electric field (SAR) distribution. At first, we used two electrodes with different dimensions (circular and rectangular). A different geometry was applied with two electrodes with different dimensions (circular and square) with which we achieved the maximum local SAR per 100W of absorbed power in the tumor region and lower total deposited power in healthy muscle and fat tissue. Using the most efficient model we performed the thermal simulation. Through the thermal simulations we confirmed that temperature distribution changes in proportion with the applied power and boundary settings. After studying the homogenous models, we confirmed the results with the realistic model of 'Ella'.

Conclusion

We have shown that starting with a simplified numerical model of the torso, it is possible to achieve an electrode configuration, which can be used with realistic patient models to improve power deposition inside the tumor while sparing healthy tissues.

References

[1] V. D'Ambrosio, F. Dughiero. Numerical model for RF capacitive regional deep hyperthermia in pelvic tumors. Medical & Biological Engineering & Computing 45:459, 2007

[2] H. P. Kok, A. N. T. J. Kotte, J. Crezee. Planning, optimisation and evaluation of hyperthermia treatments. International Journal of Hyperthermia 33(6):593-607, 2017

ARISTOTLE UNIVERSITY OF THESSALONIKI
PHYSICS DEPARTMENT

COMPUTATIONAL STUDY OF SIMPLIFIED NUMERICAL PHANTOMS INSIDE CAPACITIVE HYPERTHERMIA DEVICES

Georgios Alexiou, Theodoros Samaras

Thessaloniki 2019

Contents

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Hyperthermia

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- Hyperthermia is a condition in which the heat generated in the body cannot be dissipated by the natural thermoregulatory mechanisms. It can be induced both naturally and artificially.
- We increase the temperature in tissues from 41 to 44 °C for 30-60 minutes. It is applied once a week for several weeks. The heat is often induced by alternating electromagnetic fields.
- Hyperthermia is used in combination with chemotherapy or radiation therapy.

Biological background of hyperthermia

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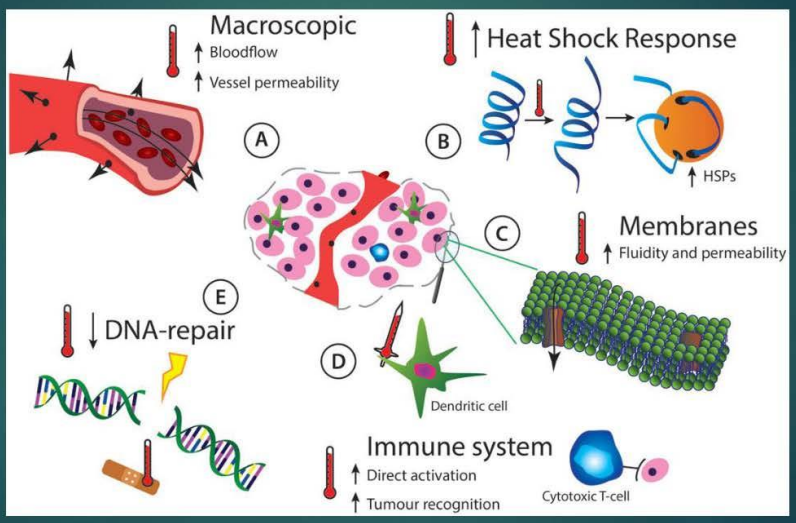

Ways of application

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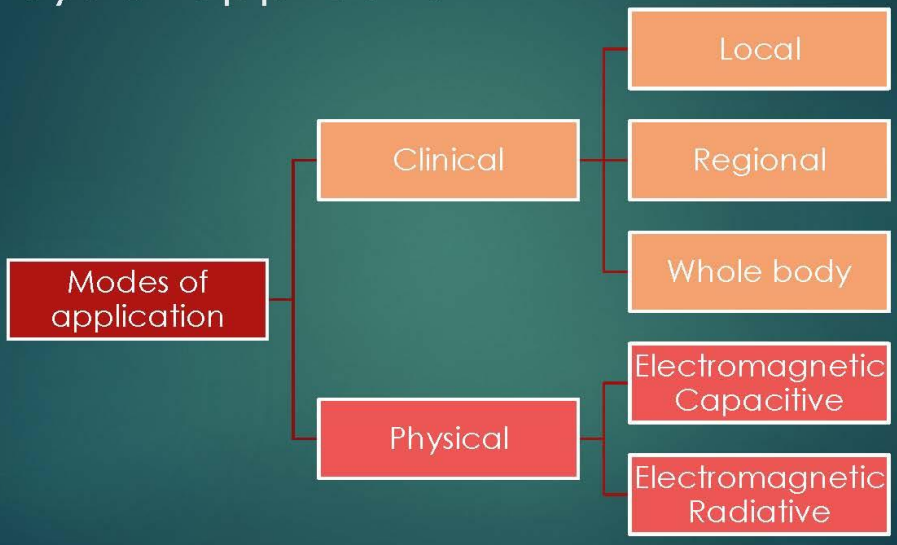

Ways of application

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The device EHY-2030 which is used in local capacitive hyperthermia (http://www.hot-oncotherm.com/about/)

Ways of application

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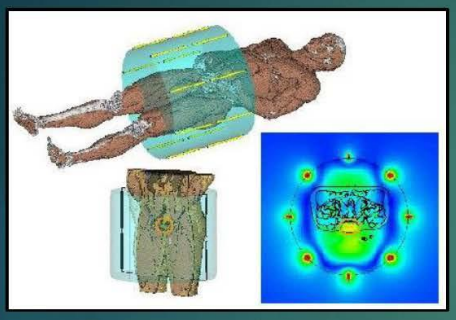

The application of regional hyperthermia (electromagnetic radiative) with the assist of ring dipole array.

The device WBH2000 for the application of whole body hyperthermia (infrared).

Treatment planning

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- **The main purpose**: To locate the exact place of **hot spots** and **cold spots**.

  This is crucial as the power is limited in great values because it causes pain in the patient.

  - Treatment planning involves the solution of systems of differential equations of some derivatives with numerical techniques because the propagation of electromagnetic radiation in human tissues is a complex phenomenon.
  - The propagation of electromagnetic radiation in human tissues is can be solved by solving Maxwell's equations numerically.

- **Result**: Finding the distribution of the electric field in tissues from which we calculate the distribution of Specific Absorption Rate (SAR).

SAR is the deposited electromagnetic power per unit mass of tissue [W / Kg].

Treatment Planning

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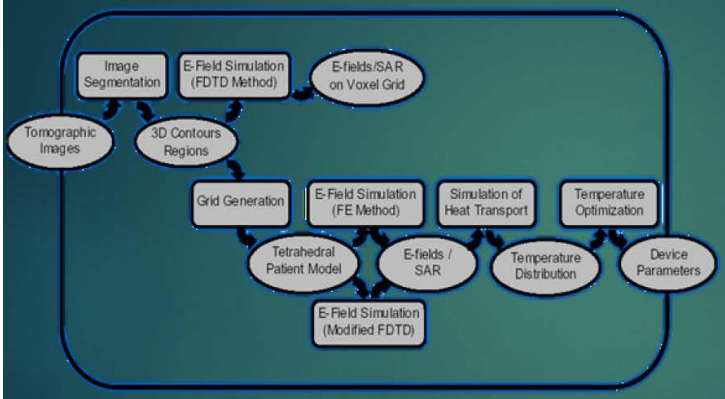

Maxwell's equations (radiative hyperthermia)

$$\nabla \times \bar{E} = -\frac{\partial \bar{B}}{\partial t} - \bar{J}_m = -\mu_o \mu_r \frac{\partial \bar{H}}{\partial t} - \bar{J}_m$$

$$\nabla \times \bar{H} = \bar{J} + \varepsilon_o \varepsilon_r \frac{\partial \bar{E}}{\partial t}$$

$$\nabla \cdot \bar{H} = \frac{\rho_m}{\mu_o \mu_r}$$

$$\nabla \cdot \bar{E} = \frac{\rho}{\varepsilon_o \varepsilon_r}$$

Bioheat Transfer Equation (BHTE)

$$\rho c \frac{\partial T}{\partial t} = k\nabla^2(T) - W_b\, c_b\, (T - T_b) + \sigma E^2 + Q_m$$

Laplace's equation (capacitive hyperthermia)

$$\nabla[\sigma(\nabla V)] = 0$$

Computational Study

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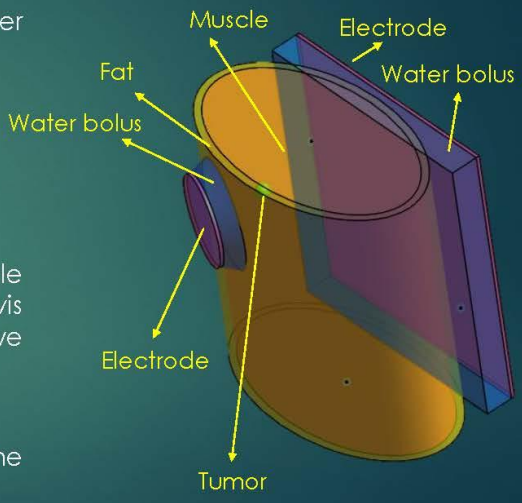
- A specific simulation platform was used in order to solve the problem:

  Sim4Life

- We used the Finite Element Method (FEM)
- We created a homogenous model with muscle characteristics (from the chest area to the pelvis area) which externally consists of fat. Also we placed a tumor inside.
- In addition we installed two electrodes with the corresponding water boluses.



Model 1

Computational Study

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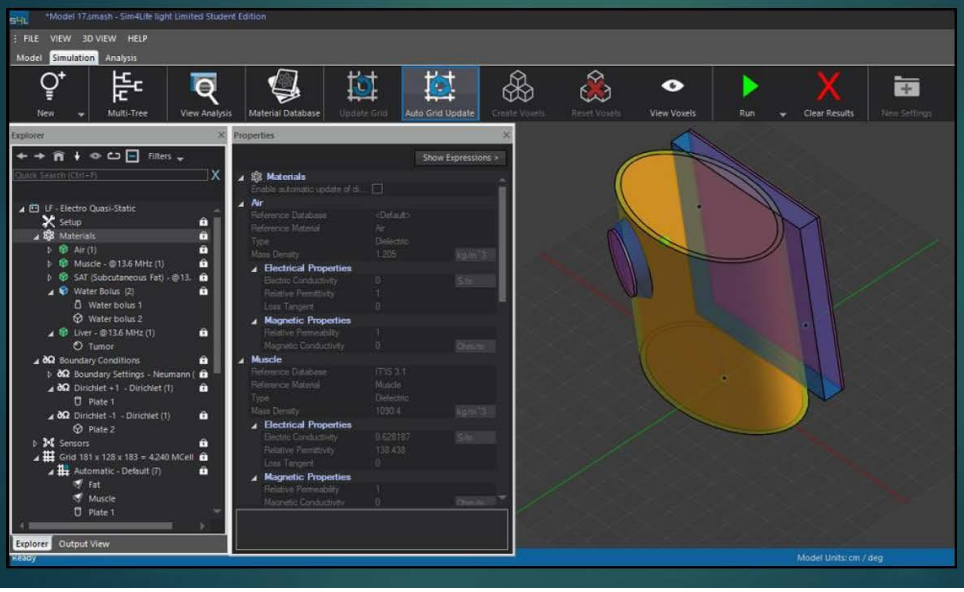

Sim4Life light 4.4.2.3851

Computational Study – Electrical Analysis

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- **Table 1.** Dielectric properties of the different parts of the model.

Body part	Density ρ (kg/ m^3)	Electric Conductivity σ_e (S/m)	Relative permittivity ε'
Muscle	1090.4	0.63	138.4
Fat	911	0.05	25.4
Tumor	1078.8	0.34	181.2
Water Bolus	1000	2	76.5

Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.0, May 15, 2018, DOI: 10.13099/VIP21000-04-0. itis.swiss/database

1st Model

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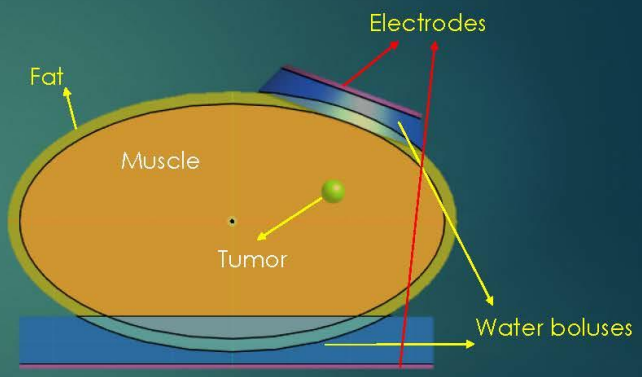
- **Voltage regulation:**
  Small circular electrode: **100 Volts**
  Large rectangular electrode: **0 Volts**
- Diameter of the small electrode: **25 cm**
- Tumor has the dielectric properties of liver and a radius of **2 cm**.



Top view of the 1st model.

1st Model

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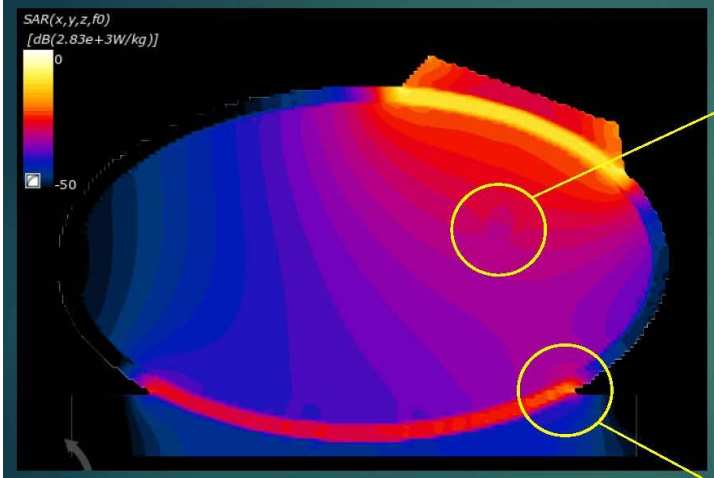

SAR distribution in the first model (top view).

1st Model

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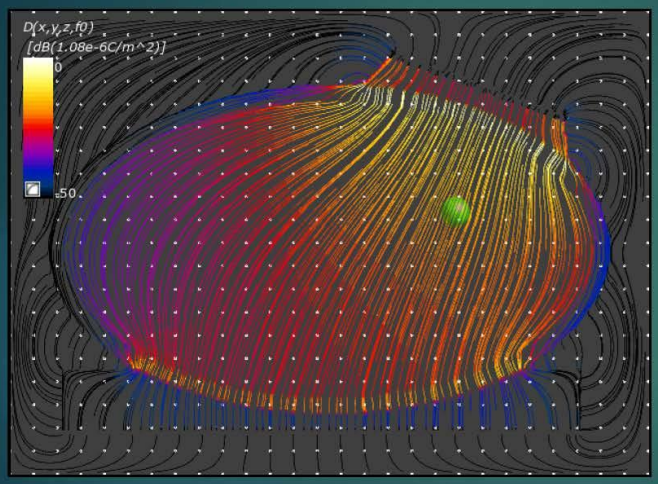

Electric field lines of the 1st model.

2nd Model

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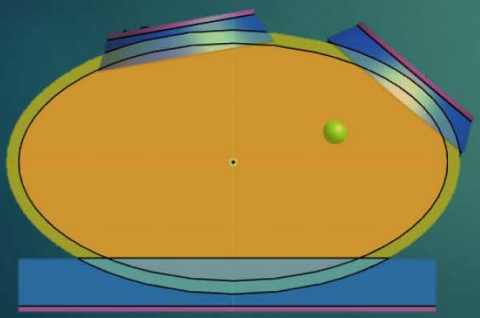
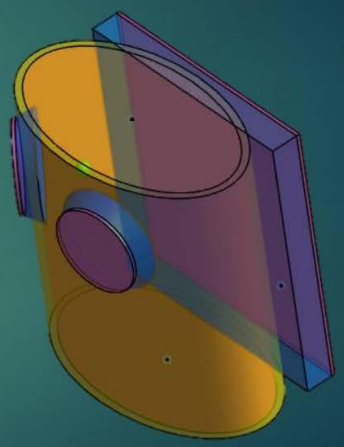
- Afterwards we did the same procedure by using 3 electrodes:
  - 1st circular electrode: +100 Volts
  - 2nd circular electrode: -100 Volts
  - 3rd electrode (rectangular): 0 Volts



Top view of the 2nd model.



Model 2

2nd Model

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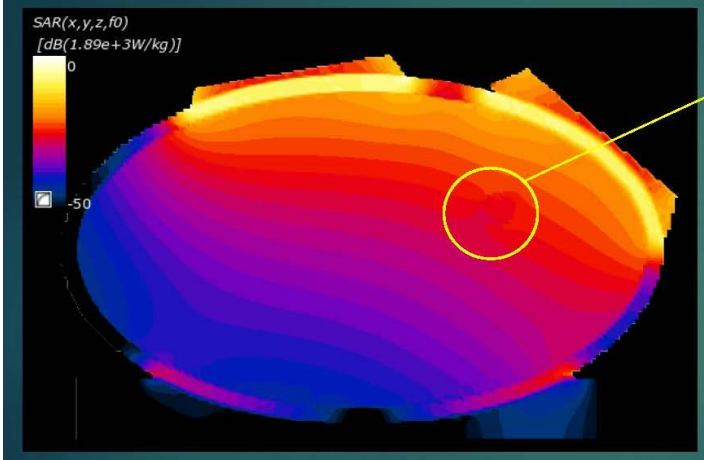

SAR distribution in the 2nd model.

2nd Model

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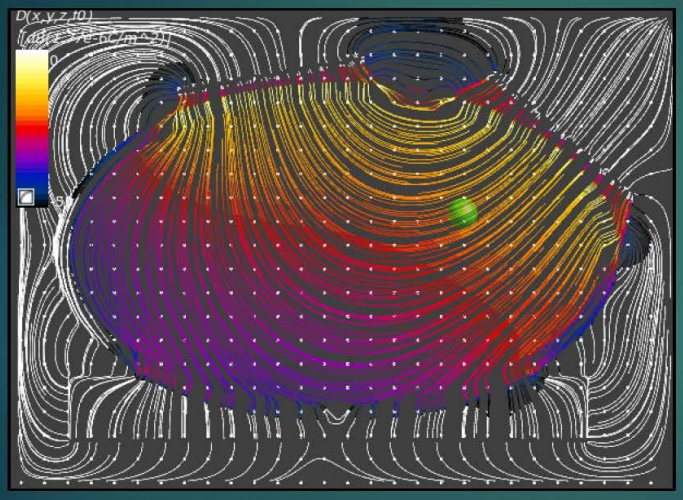

Electric field lines in the 2nd model.

3rd Model

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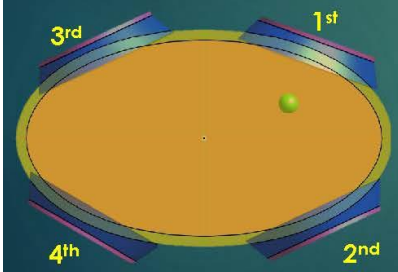
- Subsequently we replaced the large ground electrode with two small circular electrodes with the same dimensions (d = 25 cm).
  - 1st electrode: +100 Volts
  - 2nd electrode: +100 Volts
  - 3rd electrode: 0 Volts
  - 4th electrode: 0 Volts



Top view of the 3rd model.

Model 3

3rd Model

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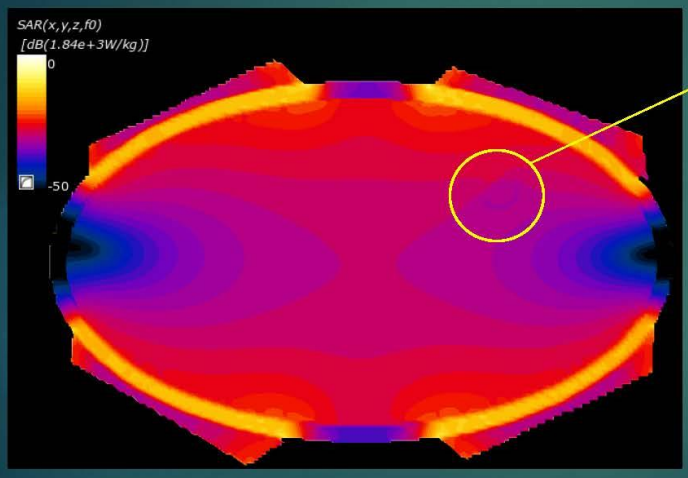

SAR distribution in the 3rd model.

3rd Model

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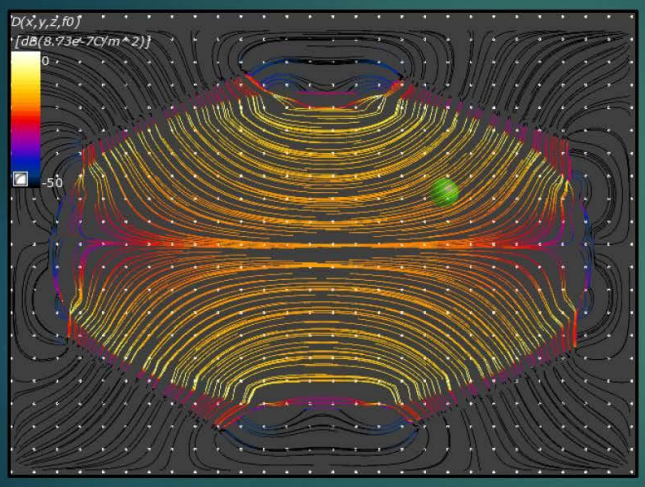


Electric field lines in the 3rd model.

Computational Study – Electrical Analysis

22

- The quantity we intended to compare in the three models is the maximum local SAR in the tumor per 100 Watts of total absorbed power.

SAR^{max} (local) x100 [(W/Kg)/100Wabs]

- **Table 2.** The results of the three previous models

Model	Number of electrodes	SAR^{max} (local) in tumor [W/kg]	SAR^{max} (local)x100 [(W/kg)/100Wabs]
1st	2	3.71	0.69
2nd	3	6.33	0.52
3rd	4	2.04	0.37

Could we improve these results ?

23

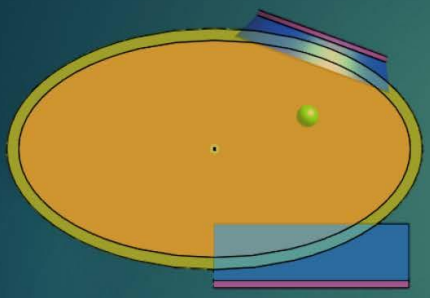
- While it may seem easy at first, raising the temperature inside the body by external means is quite a difficult task. Hot spots greatly limit the deposited power to tumors deep in the body.

- To improve the effect of hyperthermia we can reduce the size of the electrode (and water bolus) on the back of the patient, thereby forcing the field to pass through the tumor as much as possible.

- In the last model we used 2 electrodes. One is the same circular as before and the other is square with a side of 35 cm.

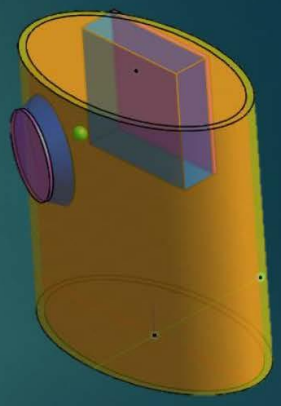
The Final Model

24



Top view of the 4th model.

- Circular electrode: +100 Volts
- Square electrode: 0 Volts



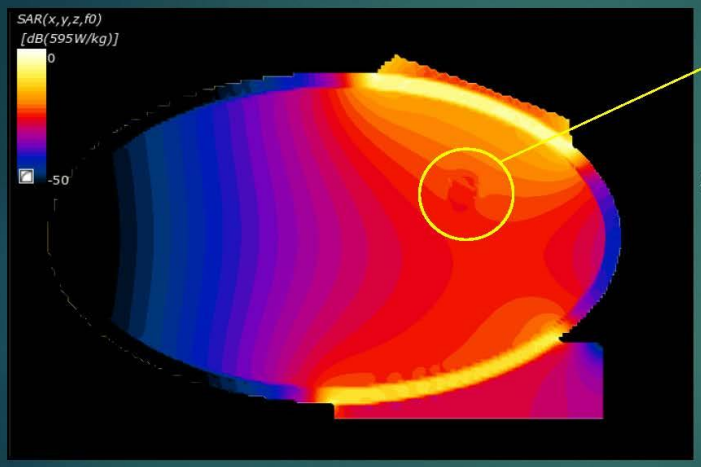
Model 4

Table 3. The results of the final (4th) model.

Model	Number of electrodes	SAR^{max} (local) in tumor [W/kg]	SAR^{max} (local)x100 [(W/kg)/100Wabs]
4th	2	2.98	0.78

The Final Model

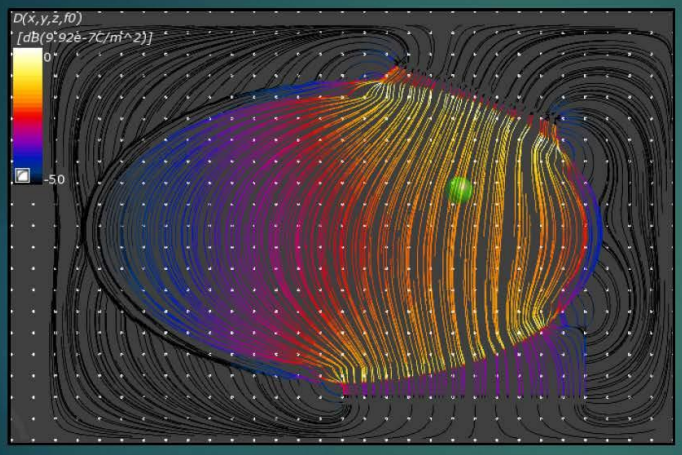
25



SAR distribution in the 4th model.

The Final Model

26



Electric field lines in the 4th model.

Computational Study - Thermal Analysis

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- Having analyzed all those models, the most efficient was the last one. This particular structure and placement of the electrodes results in better distribution of the electric field and maximizes SAR in the tumor region. Thus, the thermal analysis was made for the final (4th) model.

- **Table 3.** Thermal properties of the different parts of the model.

Body Part	Specific heat capacity (J/kg/K)	Thermal Conductivity (w/m/K)	Heat generation rate (W/kg)	Blood perfusion rate (ml/min/kg)
Muscle	3421.2	0.49	0.90	36.73
Fat	2348.3	0.21	0.50	32.70
Tumor	4181.3	0.56	0	0

Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.0, May 15, 2018, DOI: 10.13099/VIP21000-04-0. itis.swiss/database

Computational Study – Thermal Analysis

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- For the thermal analysis 4 different simulations were created. The simulation ran for two different power settings. The first one was for **400W** total absorbed power and the second one was for **1000W** total absorbed power. The simulation ran for different settings in boundary conditions on the surface of the body. At first we used **Dirichlet** boundary type and afterwards we used **Mixed** boundary type.

- **Table 4.** Temperature in the tumor for different power (W) and boundary settings

Thermal Simulation	Absorbed power (W)	Boundary condition	Tumor temperature (°C)
1	1000	Dirichlet	37-39
2	1000	Mixed	40-41
3	400	Dirichlet	37.7-39
4	400	Mixed	37-38.8

Computational Study – Thermal Analysis

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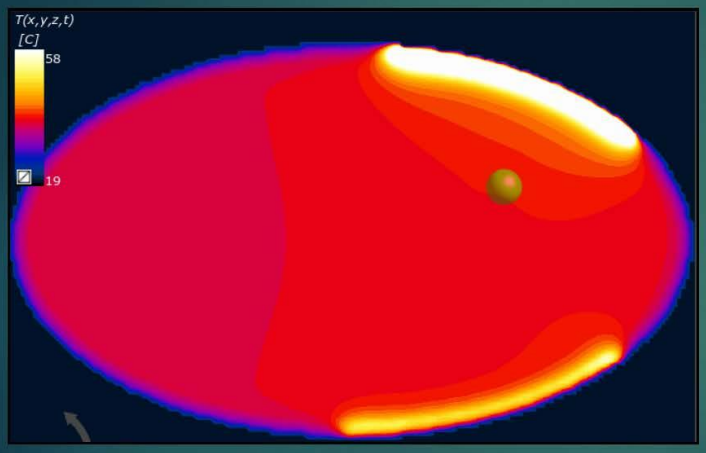


Temperature distribution in the 4th model with mixed boundary type and power of 1000W.

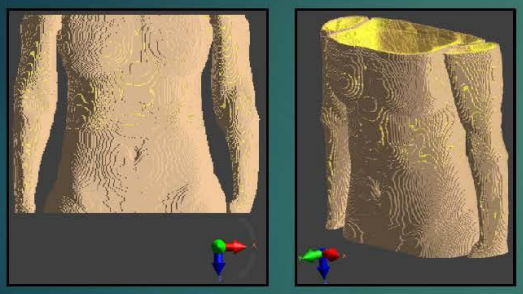
Limiting hot spots: Fat temperature 58 °C

Tumor temperature : 40 – 41 °C

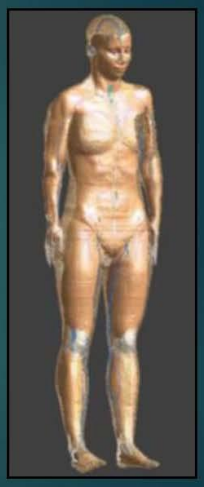
Application in a realistic model

30

- In order to understand better the effects of regional RF capacitive hyperthermia in human tissues, a computable high resolution human model was necessary to be studied.



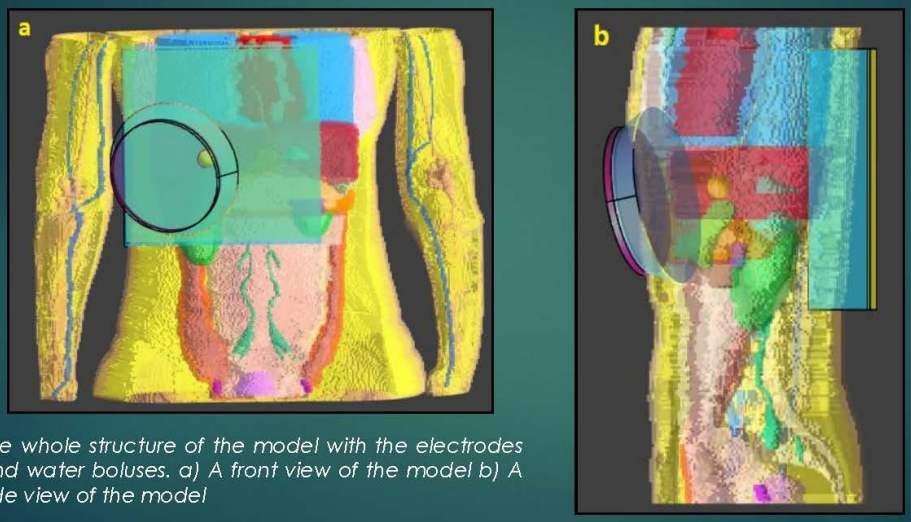
The new processed model of Ella from the upper breast area to the area of the pelvis. Skin, subcutaneous fat and fat can be observed.



The high resolution human model of Ella from Virtual Family by the IT'IS Foundation.

Application in a realistic model

31



The whole structure of the model with the electrodes and water boluses. a) A front view of the model b) A side view of the model

Application in a realistic model

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- **Table 5.** Dielectric properties of the realistic model Ella

Body part	Density ρ (kg/ m^3)	Electric Conductivity σ_e (S/m)	Relative permittivity ε'
Muscle	1090.4	0.62	138.4
Liver	1078.7	0.33	181.2
Subcutaneous fat	911	0.05	25.3
Tumor	1078.7	0.76	181.2
Skin	1109	0.23	285.2

Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.0, May 15, 2018, DOI: 10.13099/VIP21000-04-0. itis.swiss/database

Application in a realistic model

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- **Table 6.** Thermal properties of the realistic model Ella.

Body Part of Ella	Specific heat capacity (J/kg/K)	Thermal Conductivity (w/m/K)	Heat generation rate (W/kg)	Blood perfusion rate (ml/min/kg)
Muscle	3421.2	0.49	0.90	36.7
Liver	3540.2	0.51	9.93	860.4
Subcutaneous fat	2348.3	0.21	0.50	32.7
Tumor [1],[2]	3437	0.56	12	0
Skin	3390.5	0.37	1.64	106.3

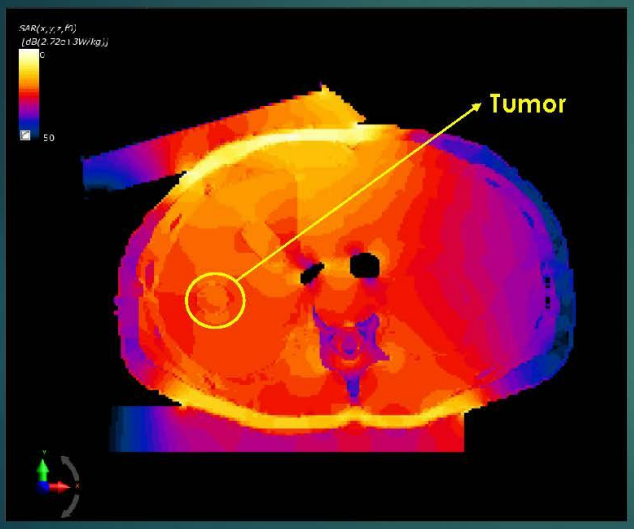
Hasgall PA, Di Gennaro F, Baumgartner C, Neufeld E, Lloyd B, Gosselin MC, Payne D, Klingenböck A, Kuster N, "IT'IS Database for thermal and electromagnetic parameters of biological tissues," Version 4.0, May 15, 2018, DOI: 10.13099/VIP21000-04-0. itis.swiss/database

We wanted a primary tumor (not metastasis) in the liver, we left all of its properties (dielectric and thermal) unaffected and changed only the electrical conduntivity to 0.76 S/m (liver cancer).

[1] Dielectric properties of VX-2 versus normal liver tissue. S.R. Smith, K.R. Foster, and G.L. Wolf,. 1986, Vols. BME-33.
[2] Zoi, Sivva. Computational study of capacitive hyperthermia with realistic models . Thessaloniki : s.n., 2019.

Application in a realistic model

34



Specific Absorption Rate in Ella with the tumor marked (energy absorption in the tumor region) top view.

Application in a realistic model

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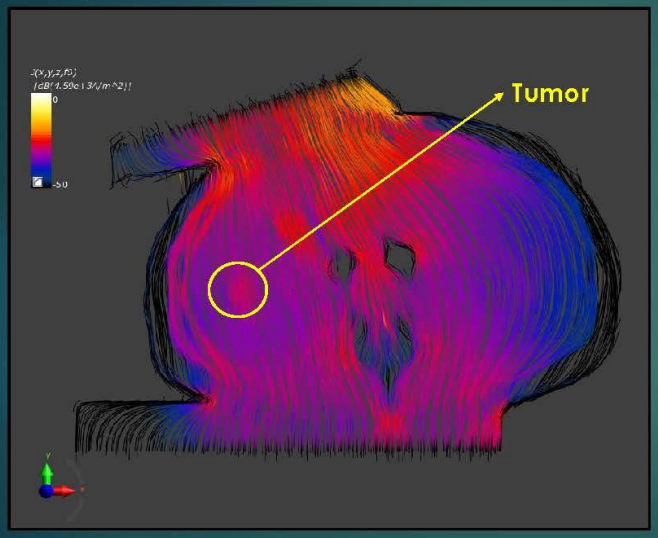

The electric field lines in Ella (top view).

Application in a realistic model

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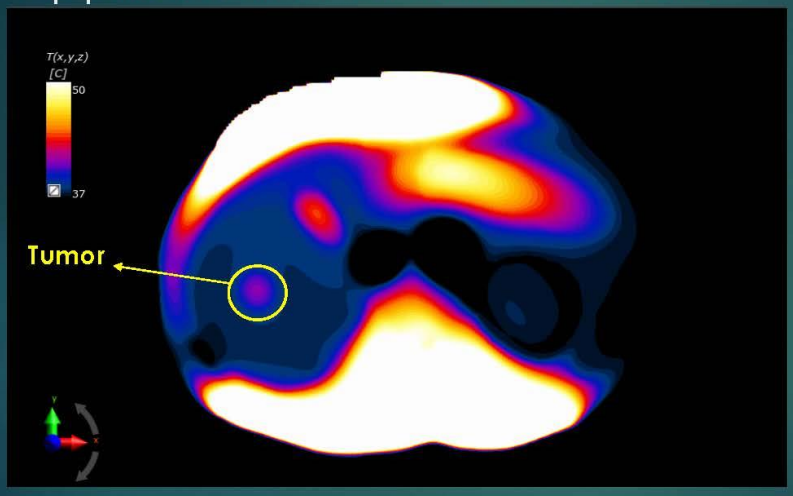

Temperature in the tumor region ranges between 41.5 and 42 °C.

Temperature distribution in the realistic model of Ella (top view).

Conclusions

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- Treatment planning is necessary in order to :
  - Increase power distribution inside the tumor region
  - Predict hot and cold spots
- Results obtained, concern only these particular homogenous models. They may change depending on the location, size and shape of the tumor.
- The optimum result occurred in the last homogenous model in which we had the maximum local SAR per 100 Watts of absorbed power.
- Through the electrical simulations it was confirmed that the number and size of the electrodes induce differences in electric field distribution thus in SAR and power distribution in the models.
- The structure and placement of the electrodes can be used in Ella but further investigation is necessary to be made in order to achieve the optimum result.

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Thank you for your attention

Efficacy and dose of local hyperthermia

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Presented at the 37th ICHS, Thessaloniki

Cite this article as:

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www.oncotherm.com/sites/oncotherm/files/2019-10/Efficacy_and_dose_of_local_hyperthermia.pdf

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

37th Conference of
International Clinical Hyperthermia Society
Thessaloniki Greece, September 19-21, 2019

Efficacy and dose of local hyperthermia

Oliver Szasz, Ph.D.
Associate Professor, St. Istvan University
CEO of Oncotherm Group

PROGRAM FINANCED
FROM THE NRDI FUND

Outline

Our goal:

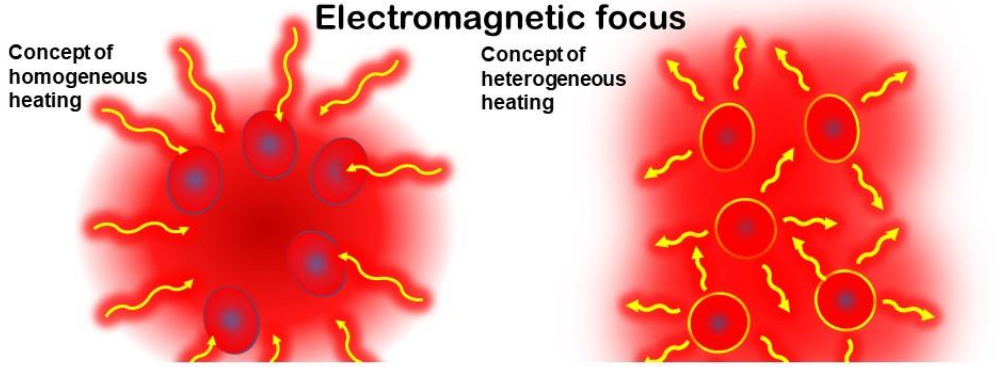
show a connection between the efficacy of the treating device and the measured dose vs measured temperature

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

Electromagnetic focus

Concept of homogeneous heating

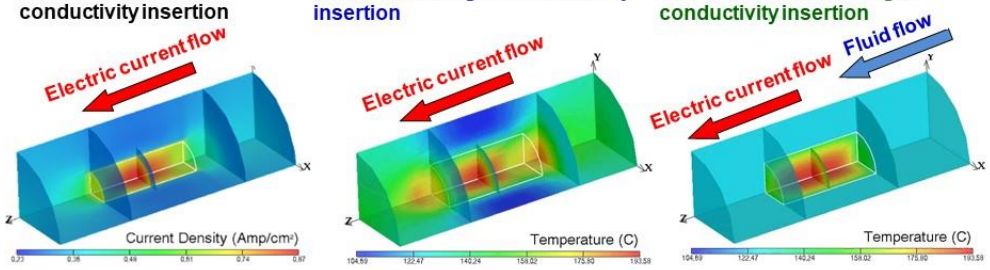
Concept of heterogeneous heating



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



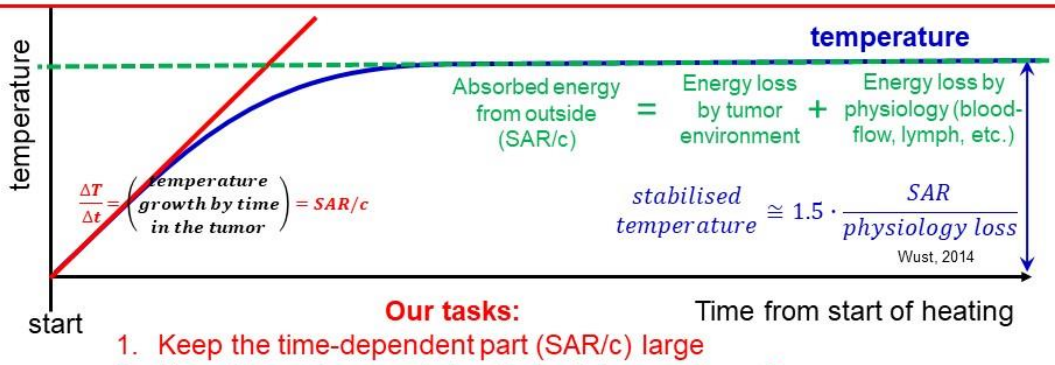
S. Salengke, S.K. Sastry: FDA approved research

Challenge of the dose of oncological hyperthermia

Pennes' equation We use its simplified description:

SAR = Specific Absorption Rate
c = specific heat= constant

$$\frac{\Delta T}{\Delta t} = \text{Temperature growth by time in the tumor} = \text{Absorbed energy from outside (SAR/c)} - \text{Energy loss by tumor environment} - \text{Energy loss by physiology (blood-flow, lymph, etc.)}$$



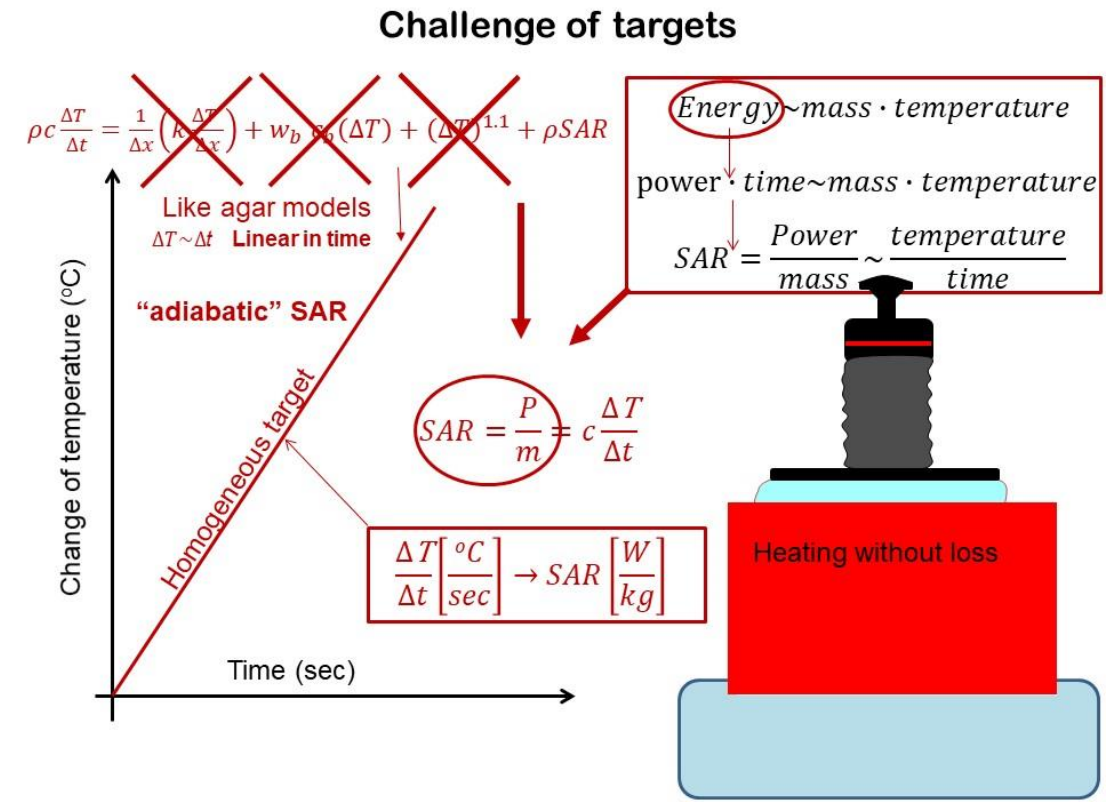
Our tasks:

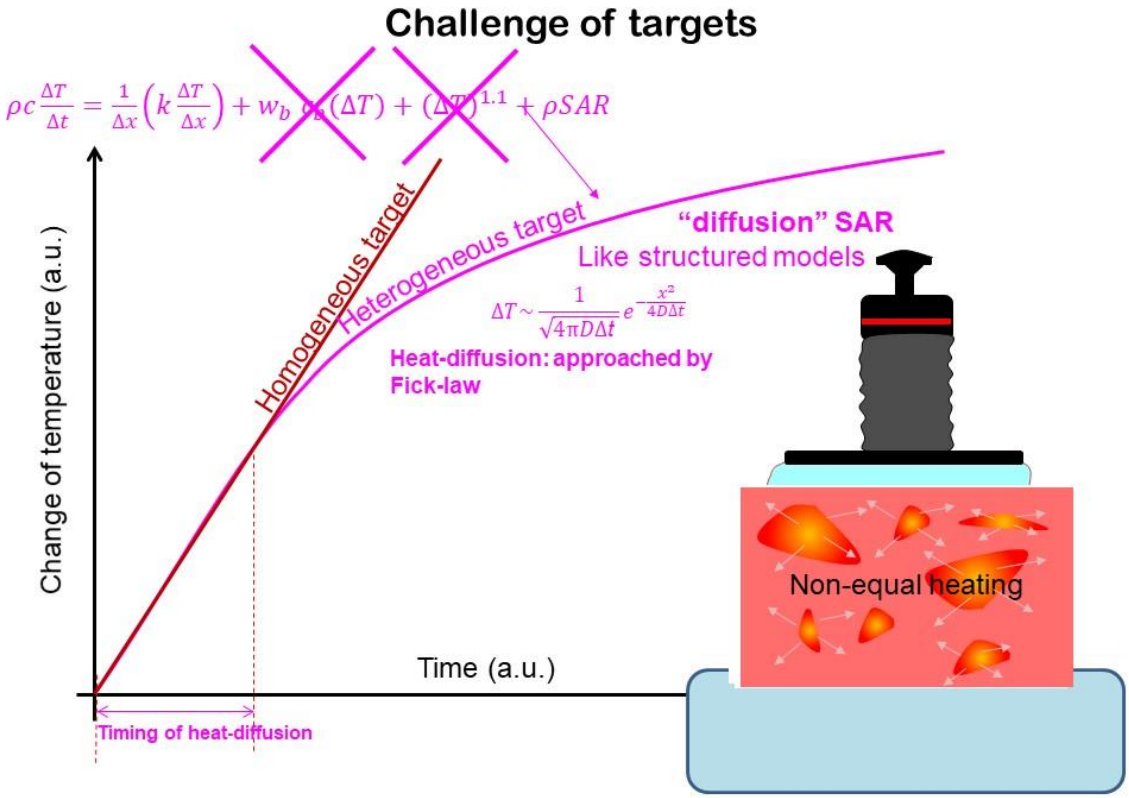
1. Keep the time-dependent part (SAR/c) large
2. Keep the environmental and physiology part small
3. Measure the dose is absorbed energy:

measured in Gy (J/kg)

(like in ionizing radiation)

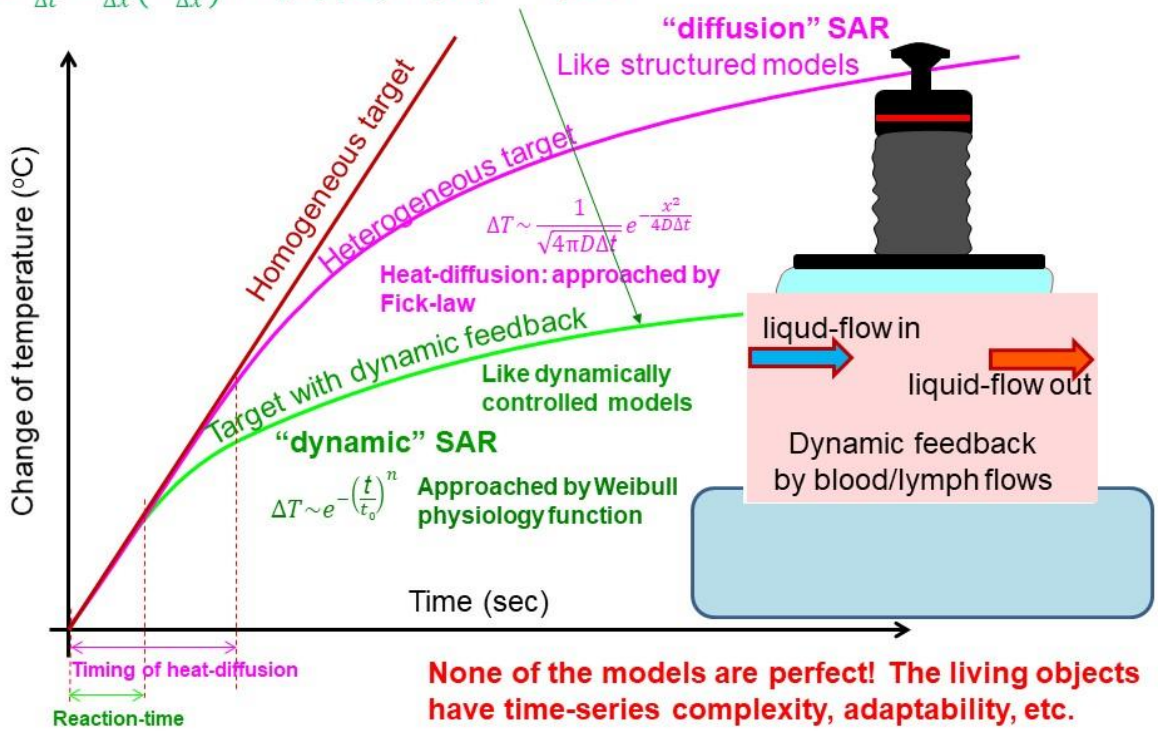
$$AE = \sum_{\substack{\{i\} \\ steady \\ -state}} c\frac{\Delta T}{\Delta t}$$


Challenge of targets
$\rho c\frac{\Delta T}{\Delta t}=\frac{1}{\Delta x}\left(k\frac{\Delta T}{\Delta x}\right)+w_b c_b(\Delta T)+(\Delta T)^{1.1}+\rho SAR$
Like agar models
$\Delta T\sim\Delta t$ Linear in time
"adiabatic" SAR
Change of temperature (°C)
Homogeneous target
Time (sec)
$Energy\sim mass\cdot temperature$
$power\cdot time\sim mass\cdot temperature$
$SAR=\frac{Power}{mass}\sim\frac{temperature}{time}$
$SAR=\frac{P}{m}=c\frac{\Delta T}{\Delta t}$
$\frac{\Delta T}{\Delta t}\left[\frac{^oC}{sec}\right]\rightarrow SAR\left[\frac{W}{kg}\right]$
Heating without loss


Challenge of targets
$\rho c\frac{\Delta T}{\Delta t}=\frac{1}{\Delta x}\left(k\frac{\Delta T}{\Delta x}\right)+w_b c_b(\Delta T)+(\Delta T)^{1.1}+\rho SAR$
Change of temperature (a.u.)
Homogeneous target
Heterogeneous target
"diffusion" SAR
Like structured models
$\Delta T\sim\frac{1}{\sqrt{4\pi D\Delta t}}e^{-\frac{x^2}{4D\Delta t}}$
Heat-diffusion: approached by Fick-law
Time (a.u.)
Timing of heat-diffusion
Non-equal heating

Challenge of targets

$$\rho c \frac{\Delta T}{\Delta t} = \frac{1}{\Delta x}\left(k \frac{\Delta T}{\Delta x}\right) + w_b\ c_b(\Delta T) + (\Delta T)^{1.1} + \rho SAR$$

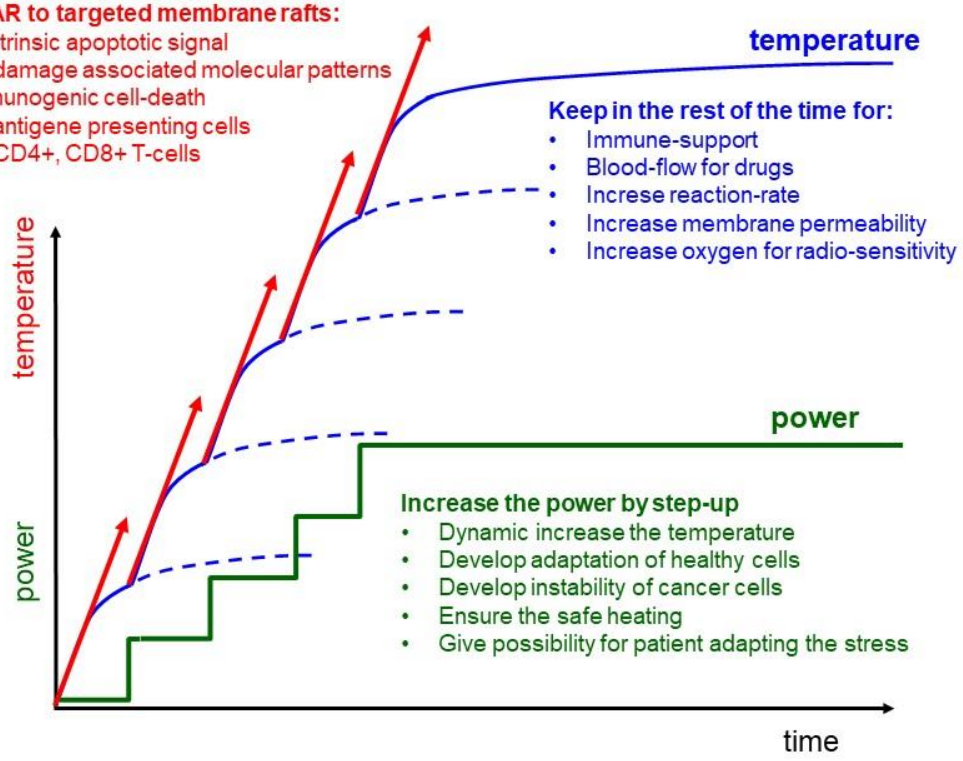


None of the models are perfect! The living objects have time-series complexity, adaptability, etc.

Our goal is completed by step-up heating

Force the SAR to targeted membrane rafts:

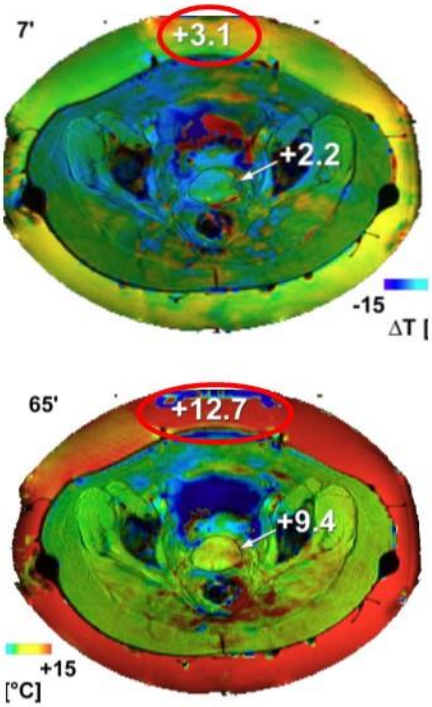
- Induce extrinsic apoptotic signal
- Produce damage associated molecular patterns
- Form immunogenic cell-death
- Produce antigene presenting cells
- Produce CD4+, CD8+ T-cells



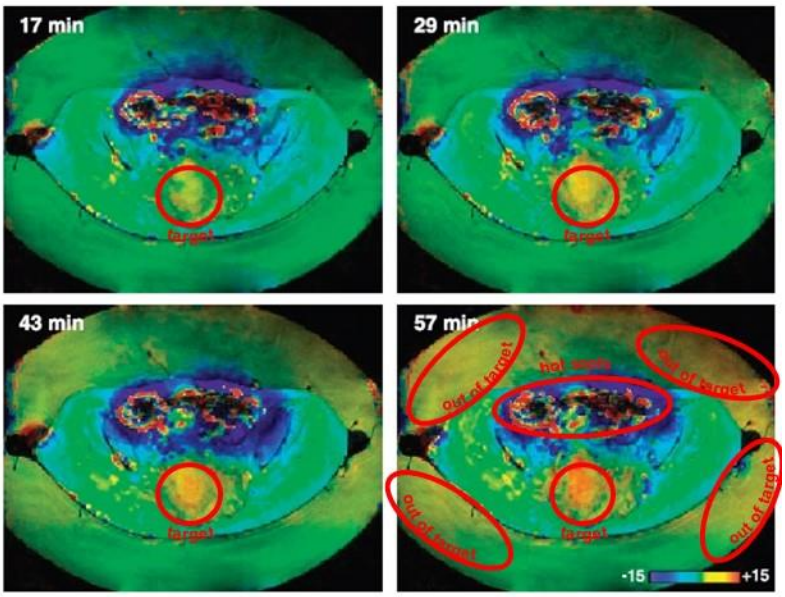
Outline

- ☑ 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)

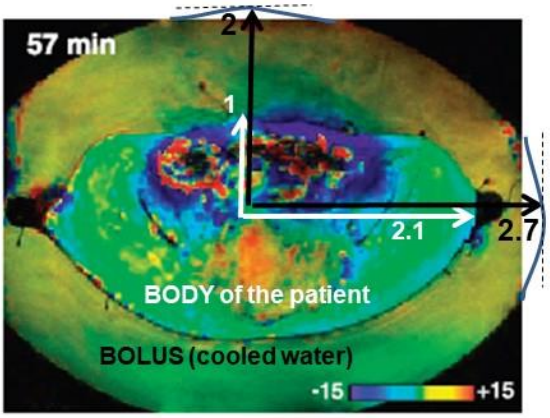


Gellermann J et al. Cancer Res 2005;65:5872-5880

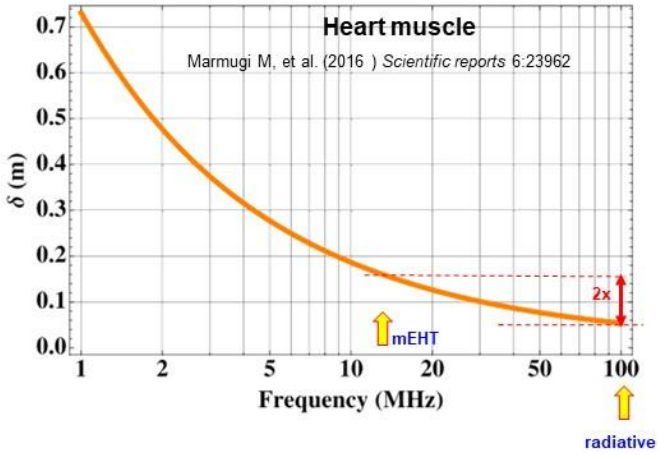
The water-bolus is heated more than the tumor. It looks like a hot-bath.

How much energy is absorbed in the tumor?

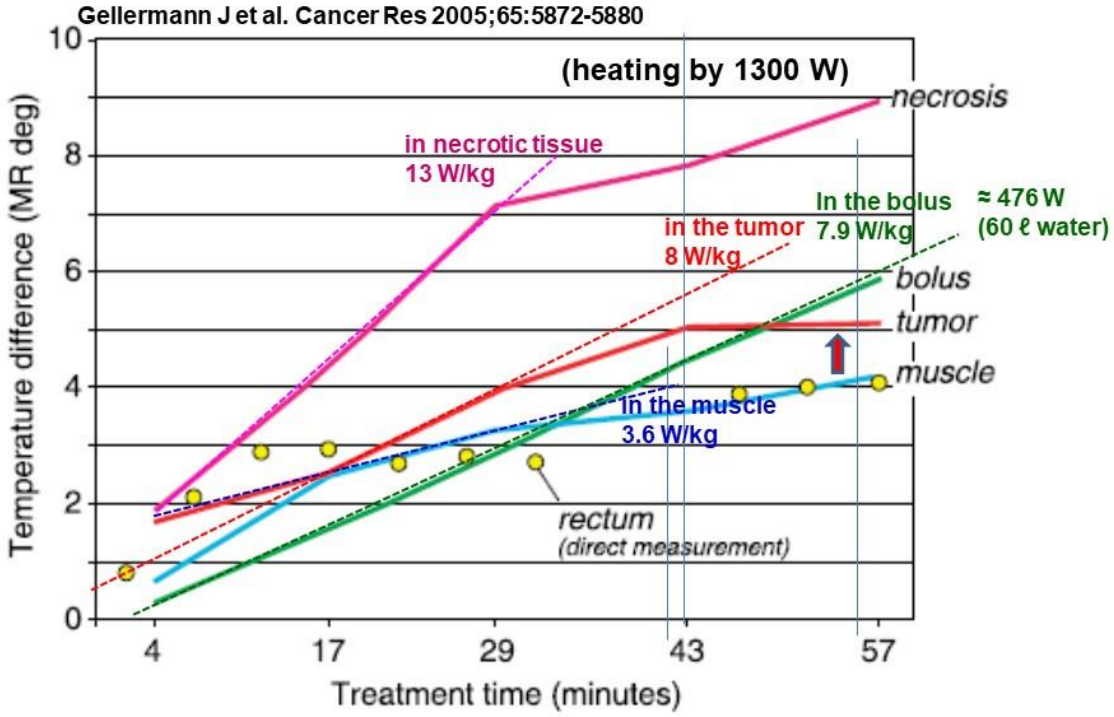
Gellermann, J. et al. (2005) *Cancer Research* 65:5872-5880.



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

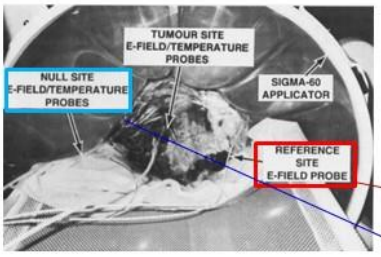
- **Radiation into the air (shielding is necessary)**
- **Cooling of the surface by large amount of water**
- **The thick bolus absorbes most of the energy**
- **The impedances for the proper surface match takes out energy**

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

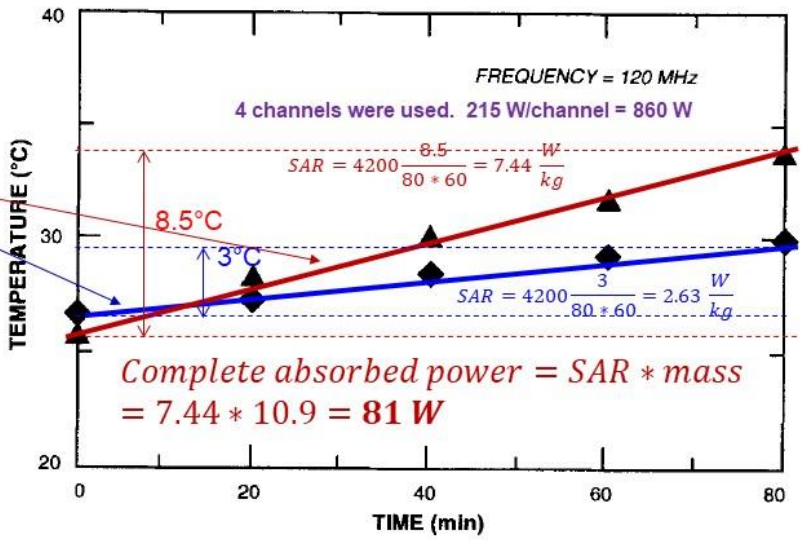
Energy loss: Serious technical challenge

Temperature measurement in a phantom



Efficacy of heating<10%

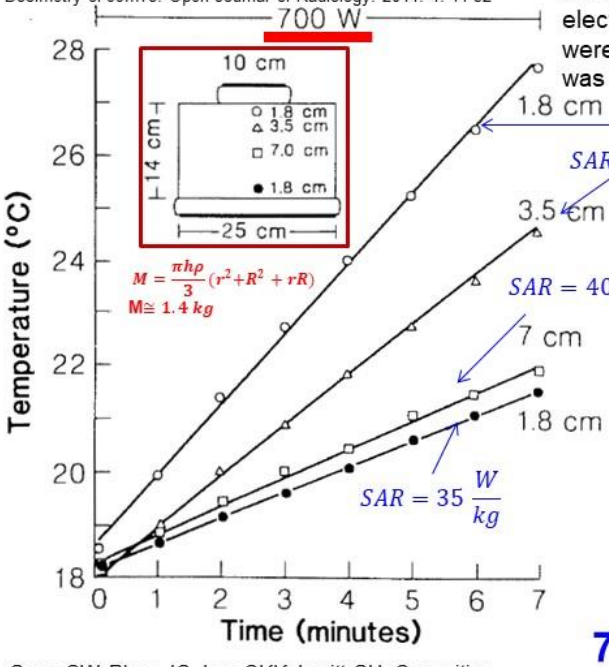
Fenn AJ. King GA. Adaptive radiofrequency hyperthermia-phased array system for improved cancer therapy: phantom target measurements. Int. J. Hyperthermia. 10:189-208 (1994)



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



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

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.

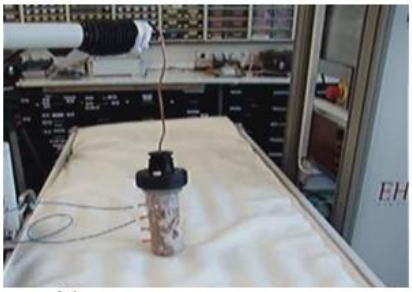
$$SAR = 4200\frac{9}{7*60} = 90\ \frac{W}{kg}$$

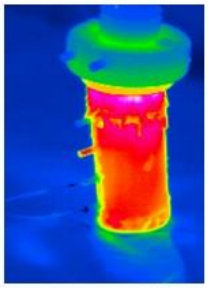
$$SAR_{average} = 70\ \frac{W}{kg}$$

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

700 W was used, efficacy is 14%

Energy loss of oncotherm: chopped meat phantom



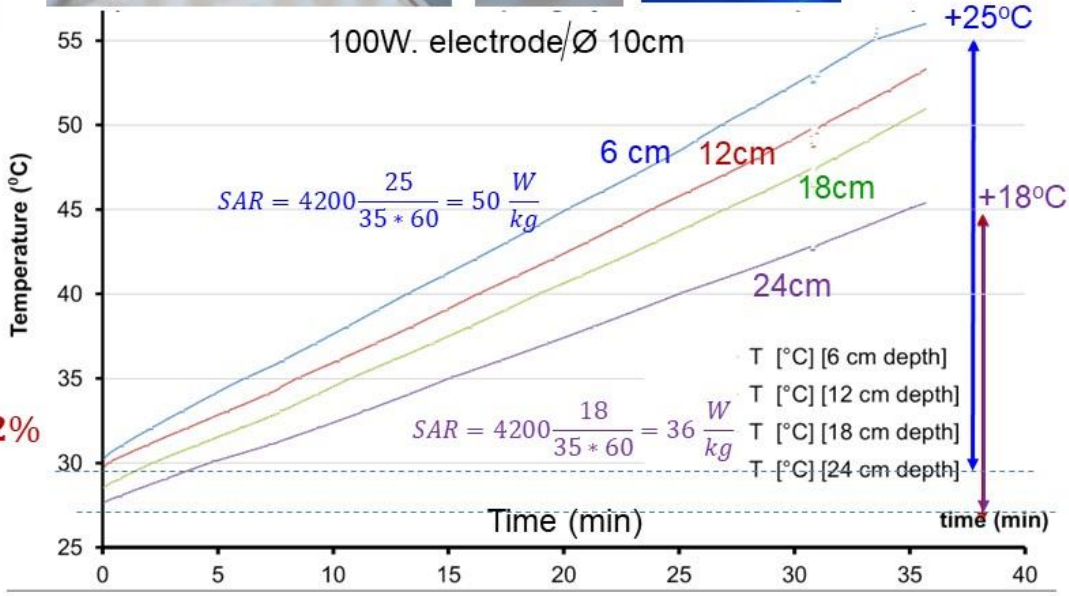


Nagy G. Meggyeshazi N. Szasz O (2013) Deep temperature measurements in oncothermia processes. Hindawi ;Conference Papers in Medicine. Volume 2013. Article ID 685264

Mass of meat $= 2.3\ kg$

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

Efficacy = 92%



Outline

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

The energy dose in clinical applications

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

With high, overall homogeneous heating (high CEM43°CT_{100}) the goal is necrosis.

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

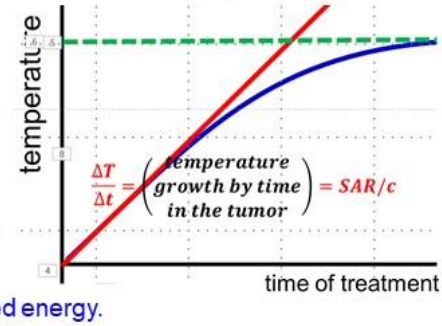
The only local elimination of malignancy gives good local control, however the malignancy is systemic.

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:

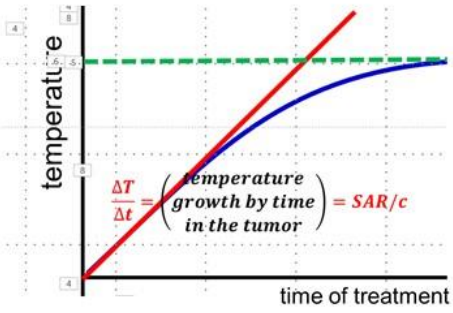
$$T_{rise} = n \sum_{time} \frac{[T_{50}(t) - 37^oC]}{t_s} \Delta t$$

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

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

Outline

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

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

Outline

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

Thank you very much for your attention

Grant support: NVKP_16-1-2016-0042

Modulated electro-hyperthermia for the treatment of relapsed brain tumors

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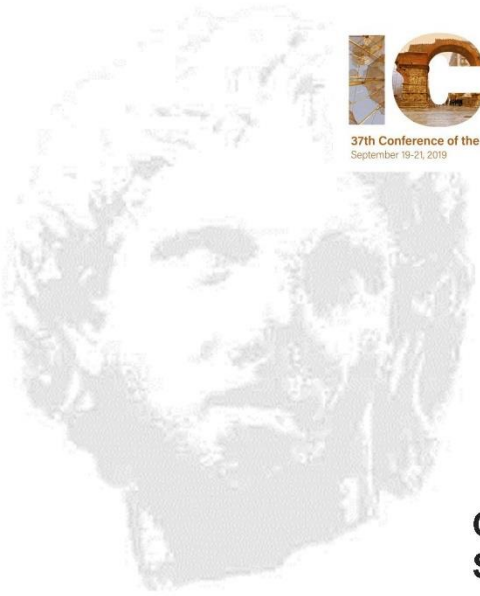
www.oncotherm.com/sites/oncotherm/files/2019-10/Modulated_electro-hyperthermia_for_the_treatment.pdf

Aim
To motor the efficacy and safety of modulated electro-hyperthermia (mEHT) for the treatment of relapsed brain tumors.

Methods
We collected data retrospectively on 164 patients that were affected by recurrent malignant brain tumors: glioma and astrocytoma. Patients were included in the study if: informed consent signed, >18 years old, histological diagnosis of malignant glioma or astrocytoma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with mEHT as palliative setting.
mEHT was performed using a capacitive coupling technique that allowed to keep the skin surface at 26 C° and to reach 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes) by applying a power of 40-150 Watts.

Results
The study sample included 164 patients with brain tumor, 115 of these (70%) had glioblastoma multiforme (GBM) and 50 (30%) had astrocytoma. mEHT was performed to 29 (25%) GBM and 28 (56%) of astrocytoma, whereas the remaining patients received the best supportive care (BSC).
Three months after mEHT, tumor response rate was 24% for GBM and 43% for astrocytoma, whereas it was 4% for GBM and 37% for astrocytoma for the BSC group. The median overall survival (OS) was 12 months (range 5-108) for GBM, and 17 months (6-156) for astrocytoma group. We observed 2 long-term survivors in the AST and 1 in the GBM group that were treated with mEHT.

Conclusions
mEHT may have promising efficacy for the treatment of relapsed malignant glioma and astrocytoma and can be a useful integrative therapy



37th Conference of the International Clinical Hyperthermia Society
September 19-21, 2019

Θεσσαλονίκη
Salonicco

Modulated electrohyperthermia (mEHT) for the treatment of Relapsed Brain Tumors

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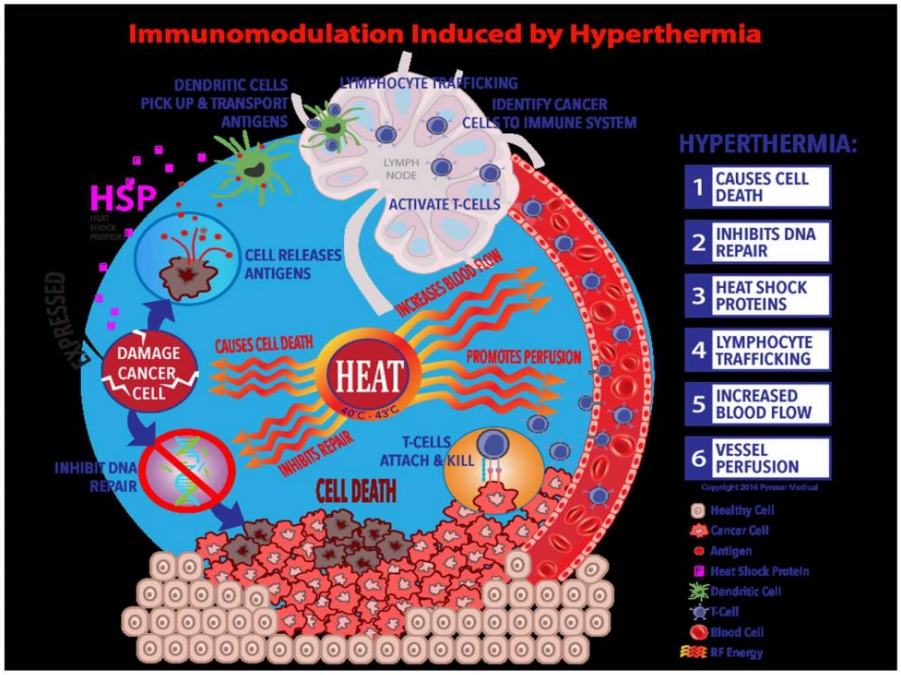


BACKGROUND

- Malignant Gliomas (MG) Therapy with hyperthermia is approved by the Food and Drug Administration .
- Studies on MG with mEHT, which combines the heat-therapy with an electric field, suggest a new way for research.
- Experts had found the mEHT method is feasible for not only palliative but reported also evidence of therapeutic response

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (I)

- Radiofrequency hyperthermia is usefull for malignat brain tumors (Tanaka R, 1987)
- Thermotherapy of recurrent malignant brain tumors is usefull (Sneed 1992)
- Favourable effects of antineoplastic agents and hyperthermia on cytotoxicity toward chronically hypoxic glioma cells (Watanabe M, 1992)
- Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/-hyperthermia for HG gliomas improves mOS with p = 0.008; hazard ratio 0.51 (Sneed, 1998)

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (II)

- Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas suggested that is a safe and well-tolerated. (Heo J , Neoplasma, 2017)
- Hyperthermia induces traslocation of apoptosis-inducing factor (AIF) and apoptosis in human glioma cell lines (Fukami T, 2004)
- Improving efficiency of adriamycin crossing blood brain barrier by combination of thermosensitive liposomes and hypertehrmia (Gong W,2011)
- Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with radiotherapy on patients with recurrent HG glioma (Mair-Hauff K, 2011)

STUDIES WHERE HT SEEMS EFFECTIVE IN MG (III)

•Non invasive intracranial hyperthermia with capacitive transference ECT intratumoral and cerebral thermometry gives favourable results (Ley-Valle, 2003) .

•Treatment of malignant glioma using hyperthermia (Sun J, 2013)

•Thermotherapy-induced reduction in glioma invasiveness is mediated by tumor necrosis factor-alpha. (Qin LJ, 2015)

•Enhanced Energy Localization in Hyperthermia Treatment Basec on Hybrid Electromagnetic and Ultrasonic System: Proof of Concept with Numerical Simulations.(Nizam-Uddin N, 2017**).**

•Pulsed-wave low-dose ultrasound hyperthermia selectively enhances nanodrug delivery and improves antitumor efficacy for brain metastasis of breast cancer.(Wu SK, 2017)

STUDIES WHERE MEHT SEEMS EFFECTIVE IN MG (I)

- Regional mEHT in combination with chemotherapy induces a mOS of 44,2 and 23,2 months in relapsed HG gliomas (Sahinbas, 2005) .
- Phase II clinical study on relapsed HG gliomas treated with mEHT reported a RR of 25% (Fiorentini, 2006).
- mEHT combined with alkylating drugs in relapsed HG gliomas reported that is tolerable and feasible (Wismeth, 2010).
- Clinical and economic evaluation of mEHT concurrent to dose-dense temozolomide regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-center German cohort trial with systematic comparison and effect-to-treatment analysis (Roussakov SV, 2017).

STUDIES WHERE MEHT SEEMS EFFECTIVE IN MG (III)

mEHT inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis. (Cha J, 2015, Int J Hyperthermia .

Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia (Fiorentini G, Int J Neurooncol Brain Tumors, Vol I, Issue 1, p11-13, 2017)

Modulated Electrohyperthermia in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: Retrospective Multicenter Controlled Study. (Fiorentini G, Integr Cancer Ther, 2019 Jan-Dec;18:1534735418812691).

AIM

to motor the efficacy and safety of modulated electrohyperthermia (mEHT) for the treatment of relapsed brain tumors

METHODS

• we collected data retrospectively on 164 patients that were affected by recurrent malignant MG.

• Patients included if informed consent signed, >18 years old, GBM or astrocytoma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with mEHT as palliative setting.

• mEHT was performed using a capacitive coupling technique that allowed to keep the skin surface at 26 C

Treatment parameters

Practical parameters	value
step-up power (from-to [W])	40-150
average energy-dose (kJ)	540
Therapeutic temperature (°C)	40-42.5
treatment time /session	60
treatment frequency (weakly)	3
treatment cycle (weeks)	8
follow-up time (months)	16

Description of the sample

Basic character (AST)	n	%
Males	24	48
Females	26	52
mEHT treated	29	58
Historical control	21	42
Data AST group	**n**	**%**
MGMT methylated	13	26
MGMT non methylated	13	26
MGMT no data	24	48
IDH1 mutated	15	30
IDH1 wild type	12	24
IDH1 no data	23	46

Description of the sample

Basic character (GBM)	n	%
Males	71	62.3
Females	43	37.7
mEHT treated	29	25.4
Historical control	85	74.6
Data of GBM group	**n**	**%**
MGMT methylated	26	22.8
MGMT non methylated	28	24.6
MGMT no data	60	52.6
IDH1 mutated	14	12.3
IDH1 wild type	20	17.5
IDH1 no data	80	70.2

The complementary therapies

Complementary therapies	All	AST		GBM	
		mEHT	no mEHT	mEHT	no mEHT
BSC	32	9	3	18	2
RT	8	0	1	0	7
CHT	0	0	0	0	0
TMZ	5	1	1	0	3
RT+TMZ	66	1	10	1	54
CHT+TMZ	1	0	1	0	0
CHT+TMZ+RT	47	14	5	10	18
CHT+TMZ+RT+FOTEMUSTINE	1	1	0	0	0
CHT+TMZ+RT+ DOTATOC	2	1	0	0	1
ND	2	2	0	0	0

The abbreviations as follows: BSC – best supportive care including dexamethasone, 18% glycerol infusion, mannitol, holistic therapy and psychosocial support, RT – radiotherapy, CHT – chemotherapy with platinum derivatives, TMZ – temozolomide therapy, ND – no data.

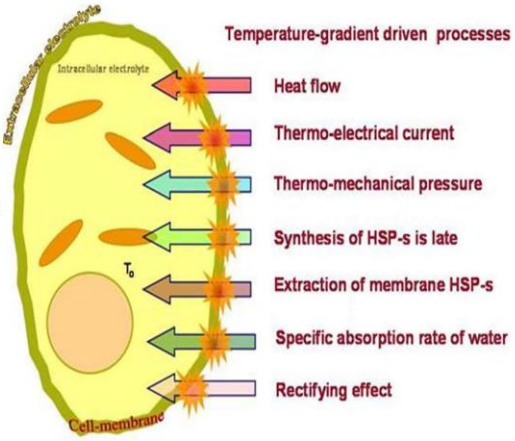
ELECTRO - HYPERTHERMIA (TRANSLATIONAL)

Regional non-invasive EHT

Selective killing effect to tumor cells – specific absorption and nano range heating (Koga 1993, Head 2000, Szasz O. 2017)

Stimulation of natural killer cell-induced apoptosis based on activation of heat-shock-proteins (Young 1990, Multhoff 2005, Baronzio 2006)

Intratumoral reduction of micro-circulation (Yoshimasa 2001).

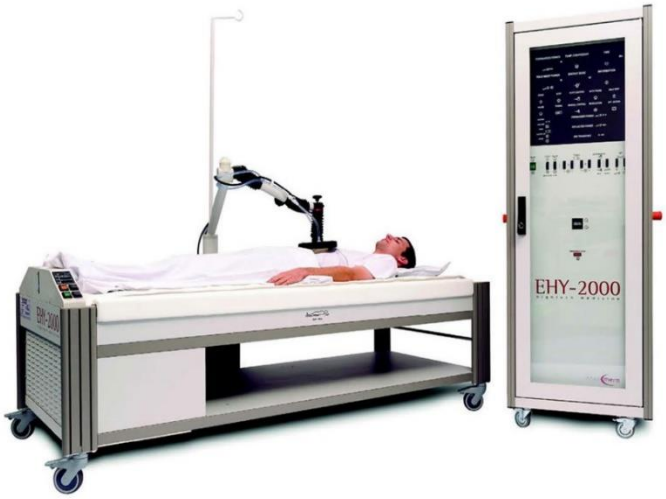


Regional EHT and ACNU have synergistic effects in a rat model (Schem, 1995)

Regional EHT plus chemotherapy have additive effects on inhibition of proliferation (Mella, 1990)

Regional EHT improves the antitumor effect of metronomic cyclophosphamide in a rat transplantable brain tumor (Borkamo 2008)

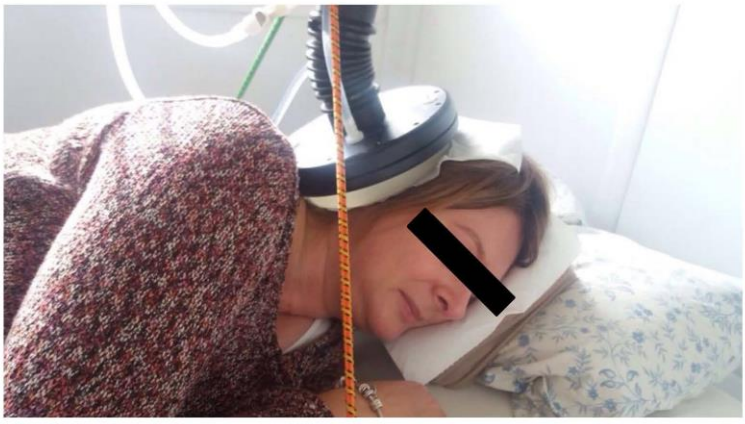
ELECTRO HYPERTHERMIA



Treating area: **REGIONAL (Deep seated tumors)**

Invasivity: **NON-INVASIVE**

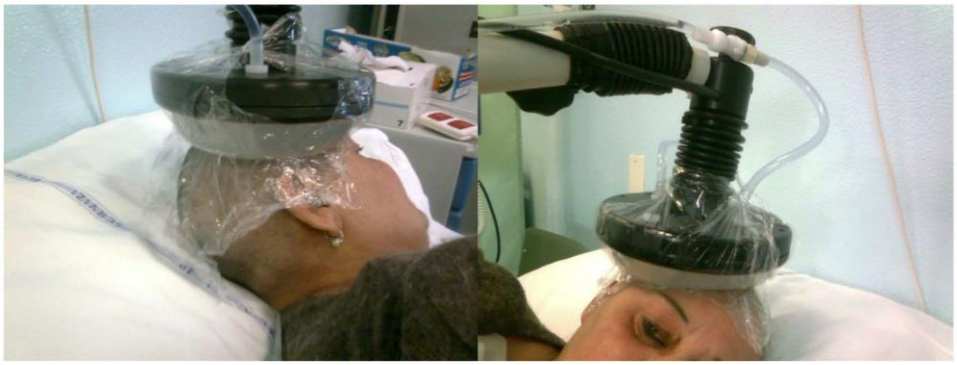
mEHT



Treating area: **Brain tumor (Pons site)**

Invasivity: **NON-INVASIVE**

mEHT



Treating area: **Brain tumor (frontal-parietal site)**

Invasivity: **NON-INVASIVE**

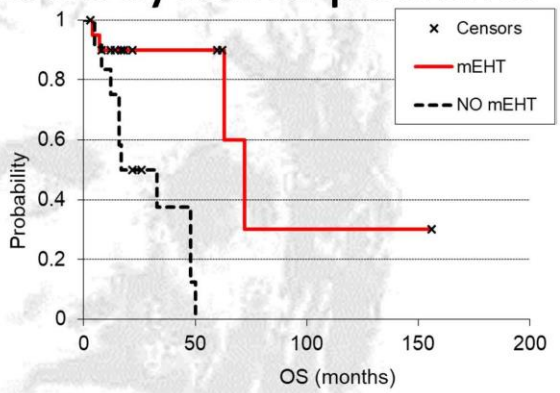
RESULTS

- 164 consecutive patients with relapsed MG, 115 of these (70%) had GBM and 50 (30%) had astrocytoma.
- mEHT was performed to 29 (25%) GBM and 28 (56%) of astrocytoma, whereas the remaining patients received the best supportive care (BSC).
- Three months after mEHT, tumor response rate was 24% for GBM and 43% for astrocytoma, whereas it was 4% for GBM and 37% for astrocytoma for the BSC group.
- The median overall survival (OS) was 12 months (range 5-108) for GBM, and 17 months (6-156) for astrocytoma group. We observed 2 long-term survivors in the AST and 1 in the GBM group that were treated with mEHT.

ASTRO response at three months

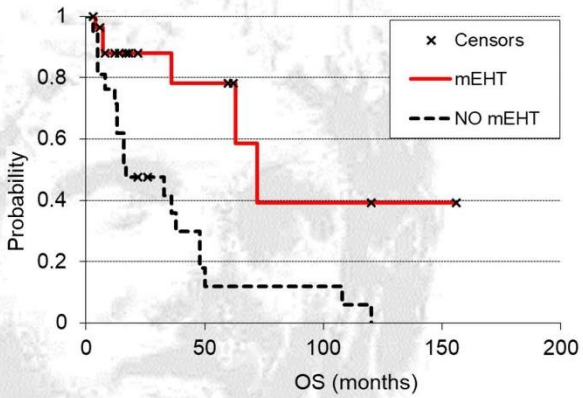
Response (AST)	mEHT		conventional		P-value
	(n)	(%)	(n)	(%)	
CR	2	6.9	1	4.8	
PR	10	34.5	6	28.6	0.0004
SD	9	31	5	23.8	
PD	6	20.7	8	38.1	0.42
NO data	2	6.9	1	4.8	-
OS median (Range)	72	(3-156)	17	(3-120)	0.0006

Duration of the response for astrocytoma patients



Median/Mean are 72/87.9 and 17/28.5 for with and without mEHT respectively. The results are statistically significant (p=0.00036). Events real/expected (Cox-mantel log-rank test) were 4/9.7 and 10/4.3 in groups with and without mEHT, respectively

OS of the AST group

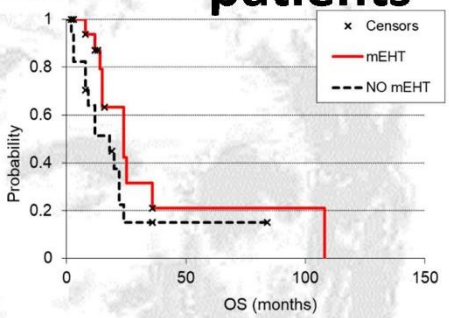


Median/Mean are 72/91.6 and 17/34 for with and without mEHT respectively. The results are statistically significant (p=0.0006). Events real/expected (Cox-mantel log-rank test) were 6/14.3 and 19/10.7 in groups with and without mEHT, respectively.

GBM response at three months

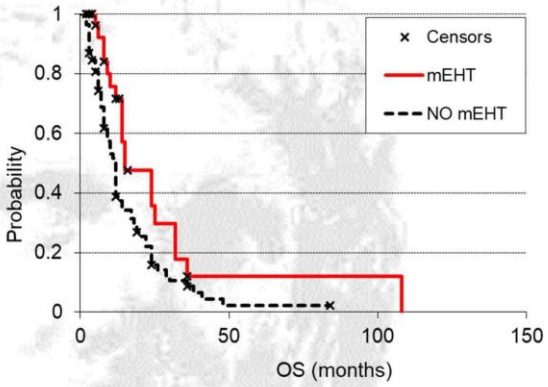
Response (GBM)	mEHT		conventional		P-value
	(n)	(%)	(n)	(%)	
CR	1	3.4	2	2.4	
PR	6	20.7	2	2,4	0.123
SD	11	37.9	13	15.3	
PD	11	37.9	63	74.1	0.858
NO data	0	0.0	5	5.9	-
OS median (Range)	15	(2-108)	12	(2-84)	0.026

Duration of the response for GBM patients



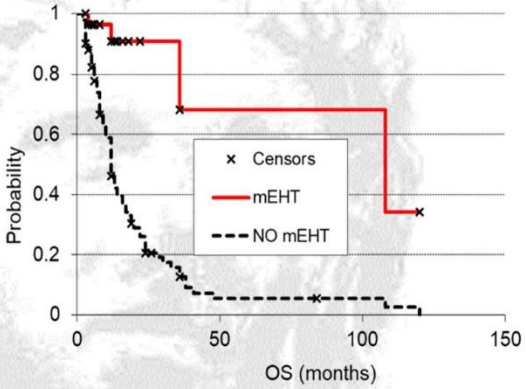
Median/Mean are 24/39.1 and 18/23.9 for with and without mEHT respectively. The results show the difference, but they are statistically not significant (p=0.123). Events real/expected (Cox-mantel log-rank test) were 10/13.4 and 13/9.6 in groups with and without mEHT, respectively.

OS of GBM group



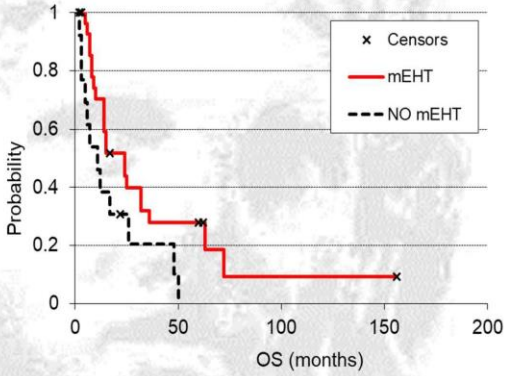
Median/Mean are 15/29 and 12/15.8 for with and without mEHT respectively. The results are statistically significant (p=0.026). Events real/expected (Cox-mantel log-rank test) were 19/28.2 and 68/58.8 in groups with and without mEHT, respectively.

Effect of temozolomide (TMZ) for glioblastoma patients



Complementary therapy contains TMZ. Median/Mean are 108/86.7 and 12/20.5 for with and without mEHT respectively. The results are statistically significant (p=0.00001). Events real/expected (Cox-mantel log-rank test) were 4/20.4 and 75/58.6 in groups with and without mEHT, respectively

Complementary therapy without TMZ



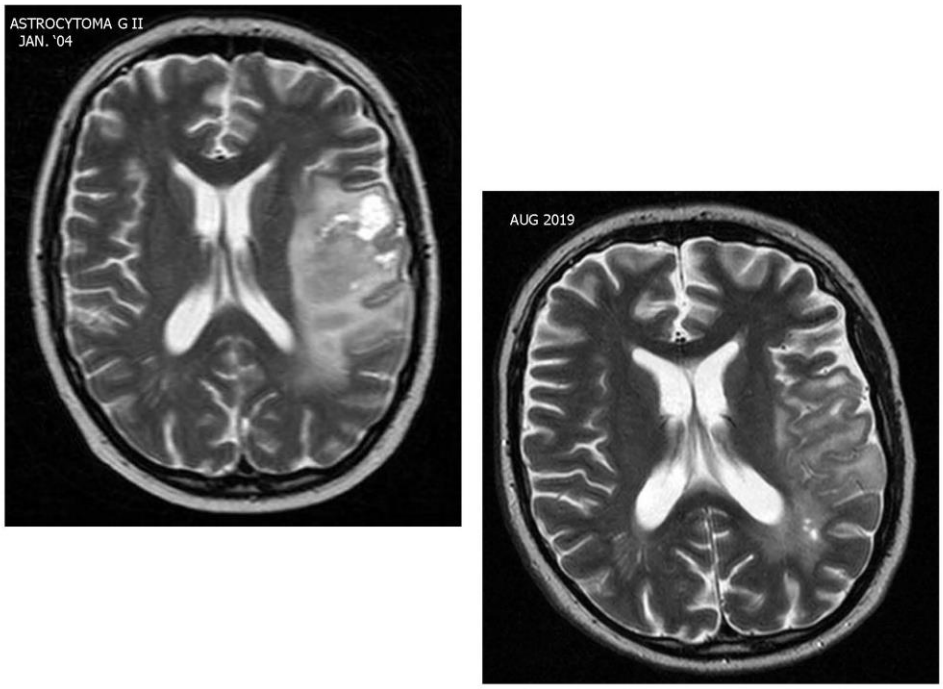
Median/Mean are 24/38.9 and 11/17.85 for with and without mEHT respectively. The results are statistically significant (p=0.039). Events real/expected (Cox-mantel log-rank test) were 21/25.8 and 12/7.2 in groups with and without mEHT, respectively.

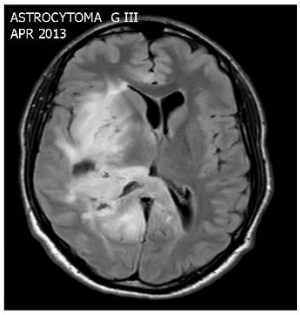
Safety

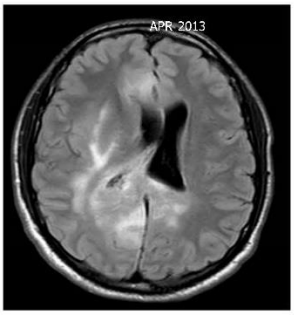
• The safety profile was confirmed by the small total number of adverse events (5%).

• mEHT toxicity was mild (G1).

• We observed one (1%) head pain, one (1%) scalp burn, five (3%) epilepsy that was resolved with medication including diazepam 10 mg in 100 ml of saline and levetiracetam in tablets without any further attack




ASTROCYTOMA G III
APR 2013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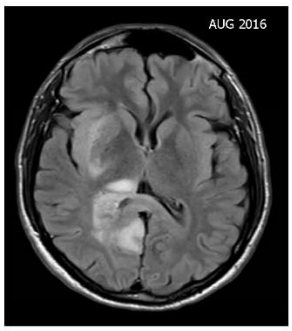
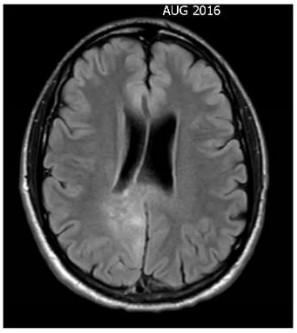

AUG 2016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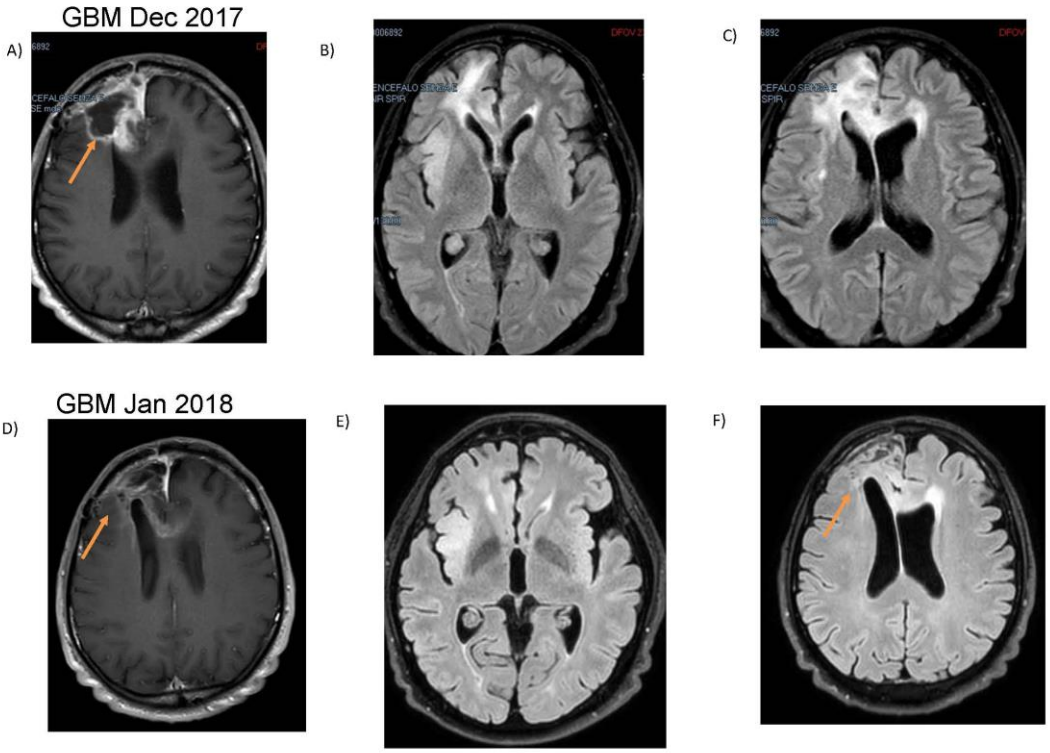
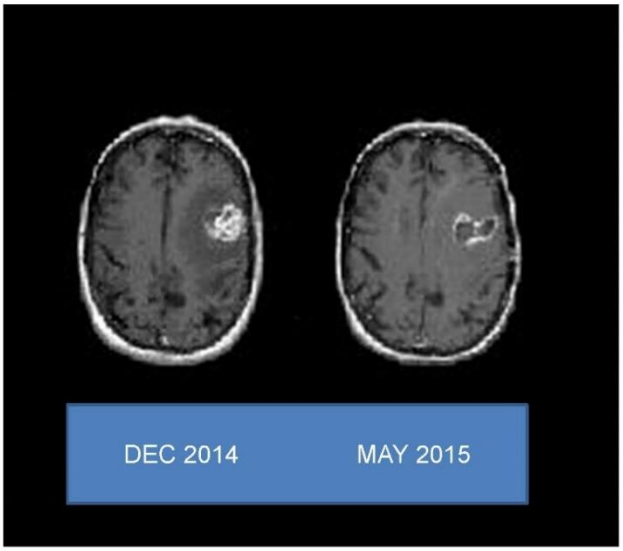
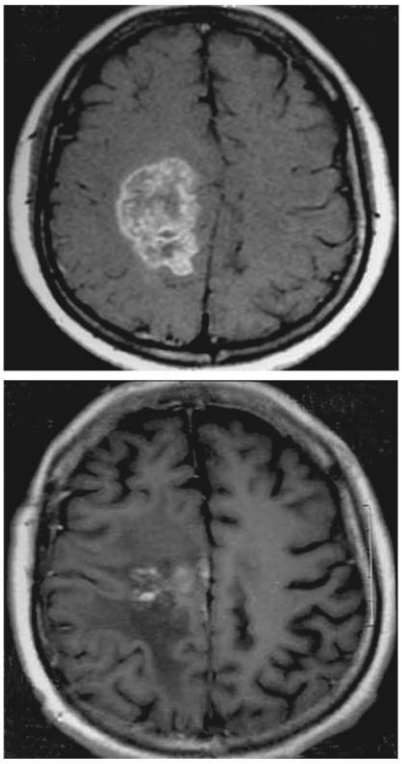

GBM Dec 2017
A)
B)
C)
GBM Jan 2018
D)
E)
F)

RELAPSED GBM G III Partial Remission





RELAPSED GMB
OCT 2010

RELAPSED GMB
FEB 2011

Partial remission

CONCLUSION

- mEHT was a safe and effective treatment of recurrent MG as integrative therapy.
- Both AST and GBM had higher tumor response rates after mEHT than after BSC, reporting few- and mild-intensity adverse events.
- The survival and quality of life were improved as well.
- The main limitation of the study was the retrospective data collection, for this reason, further randomized prospective studies with larger number of patients are also required.

ευχαριστίες

Thank you

Potential Application of Neoadjuvant Chemotherapy Plus Modulated Electro-hyperthermia (mEHT, trade name: Oncothermia) Among Patients With Advanced Cancer: Retrospective Clinical Analysis Of Single Hospital Experiences

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Presented at the 37th ICHS, Thessaloniki

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www.oncotherm.com/sites/oncotherm/files/2019-10/Potential_Application_of_Neoadjuvant.pdf

Introduction

Despite aggressive local therapy, patients with locally advanced cancer are at significant risk for local recurrences and systemic metastases. The risk of local recurrence after operation is largely dependent on clinical stage. The predominant cause of metastatic recurrence is occult micrometastases. More effective treatment methods are therefore needed for local and systemic controls. For these purposes, hyperthermia is limitedly applied to locally advanced sarcoma or high risk peritoneal carcinomatosis patients with perioperative chemotherapy. But because of some side effects and low patient compliance neoadjuvant chemotherapy with classic hyperthermia has limitations. In preclinical and clinical data modulated electro-hyperthermia(mEHT) not only suppress local tumor growth but also demonstrate immunologic effects at distant sites with negligible side effects. For this reason, there is interest in combining locoregional mEHT and systemic chemotherapy before definitive surgical treatment.

Objectives

The primary objective is whether the neoadjuvant chemotherapy plus mEHT in patients with various locally advanced cancer is feasible. The secondary objective is evaluation of safety and side effects of this treatment.

Material/Methods

This is a single hospital, observational and retrospective clinical study. We reviewed the medical records of all patients who underwent mEHT at Oasis Cancer Hyperthermia Research Center between January 2017 and July 2019. The feasibility of patients treated with neoadjuvant chemotherapy plus mEHT as well as safety and side effects were investigated. The chemotherapy regimens differed from cancer types and the university hospitals they treated.

Results

Data from 203 eligible patients were collected. The number of patients by cancer types were 101 breast, 26 stomach, 13 thyroid, 12 colon, 10 rectum, 9 lung, 8 ovary, 6 liver, 5 cervix, 5 sarcoma, 5 pancreas and 3 oesophageal cancer patients respectively. Among them 21 patients showed receiving neoadjuvant chemotherapy with mEHT treatment. The majority of these patients had stage III or IV disease at diagnosis. The number of patients by cancer types were 11 breast, 4 rectum, 3 stomach, 2 ovary and 1 colon cancer patients. No patients showed progressive disease during this treatment and all of them could done operation. Two breast cancer patients showed complete response. The side effects were tolerable and compatible with the type of chemotherapy regimen they received. No additional side effects related to the treatment of mEHT was noted.

Conclusion

There is no clinical trial whether neoadjuvant mEHT with chemotherapy treatment of localized advanced cancer feasible. Our retrospective analysis demonstrates that this treatment method can be given safely before operation to patients with locally advanced cancers. Although patient numbers were small all 21 patients could receive operation without disease progression. We believe that this neoadjuvant hyperthermic chemotherapy can be offered to patients with locally advanced cancers. Further studies are needed to evaluate the patient survival.

오아시스 요양병원 닥터 오아시스

Potential Application of Neoadjuvant Chemotherapy Plus modulated Electro-hyperthermia(mEHT, trade name:Oncothermia) Among Patients With Advanced Cancer: Retrospective Clinical Analysis Of Single Hospiatal Experiences

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오아시스 요양병원 닥터 오아시스

Advanced Cancers; Problems

- Early systemic micrometastasis in some cancers correlate with poor long-term survival(LTS) and quality of life(QOL)*
- High locoregional recurrences negatively impact both LTS and QOL

*N Engl J Med 2009; 361:653-663

오아시스 요양병원

NACT*; Scientific Background

- Preoperative chemotherapy ("neo-adjuvant chemotherapy," NACT) more beneficial than postsurgical adjuvant chemotherapy (ACT)
  - better overall survival (OS)
  - improve and/or optimize the surgical approach
  - monitor apparent response to adjust the specific regimen
  - Easy to perform phase II trials or to identify biomarkers
- Enough evidences?

NACT*; Neoadjuvant Chemotherapy

오아시스 요양병원

Possible benefits of NACT

Potential benefit	Proven with high levels of evidence?
Prolongation of overall survival	No
Optimize surgical approach	Yes
Modify chemotherapeutic regimen	No
Add further chemotherapy	No
Phase II testing of new drugs, new regimens, or compare regimens	Partially
Identify new biomarkers of response or toxicity	No

JNCI Monographs, 2015, 51, 36-30

오아시스 요양병원

mEHT*; Scientific Background

- Direct local cytotoxic effects and indirect systemic immunologic effects
- Few side effects and good patient compliance
- Expect synergistic effects when doing with NACT

*modulated Electro-hyperthermia(mEHT, trade name:Oncothermia)

오아시스 요양병원

mEHT; Korean Situations

- Use mEHT at large numbers of small integrative oncology hospitals but small numbers at large academic hospitals including Univ. Hospitals
- Barriers obtaining clinical data, doing clinical trials
- May have great potential in collecting data or performing clinical trials

오아시스 요양병원 닥터 오아시스

NACT + mEHT; Purposes

- Feasibility of NACT + mEHT among patients with advanced cancer by checking efficacy and TEAE*
- Identification of available cancers for NACT + mEHT research in Korea

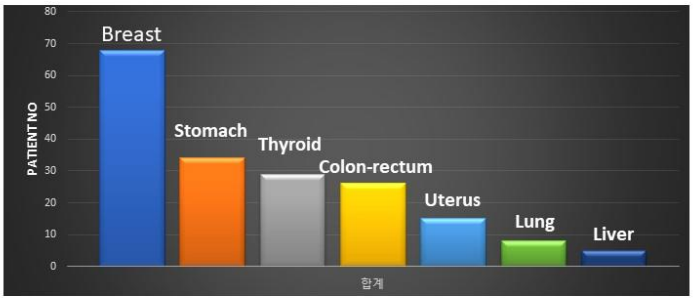
*TEAE; treatment-emergent adverse event

오아시스 요양병원 닥터 오아시스

2016.12.20 established

Types of Cancer

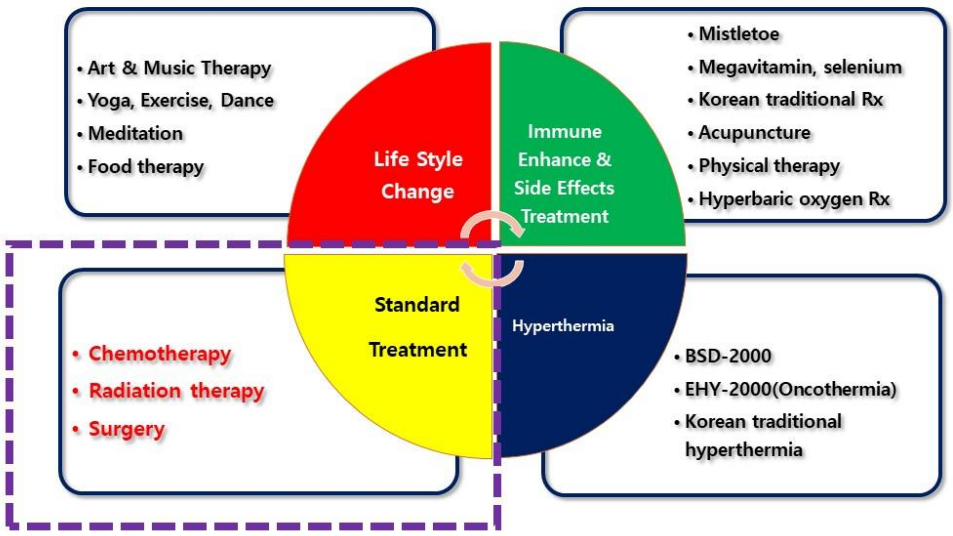
- 70~80 patients admission
- Major cancer types; breast, stomach, thyroid, colon-rectum and uterus



Admission numbers, 2017

오아시스 요양병원

Oasis Cancer Care Program



Multidisciplinary Integrative Medical Care

오아시스 요양병원 닥터 오아시스

Cancer Hyperthermia Research Center

오아시스 요양병원

Life Style Change

오아시스 요양병원

Study Design

- Retrospective chart review the patients who received mEHT from Jan. 1, 2017, to July 31, 2019
- Reviewed through the hospital's electronic medical record database
- All clinical encounters, basic demographic information, surgery and pathology reports, and treatment history
- Inclusion criteria: age ≥18 years, mEHT treatment No ≥ 12, who intend surgery when initially admit

NACT + mEHT; Patient Characteristics

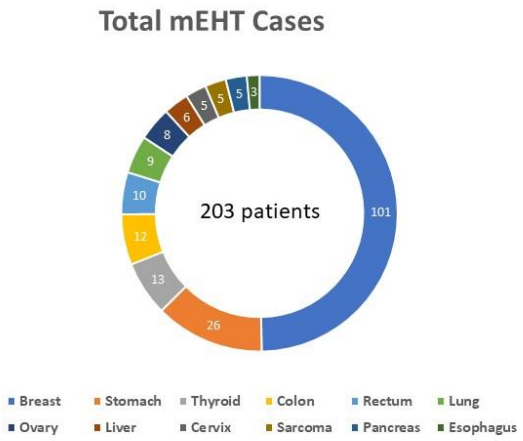
mEHT Tratment

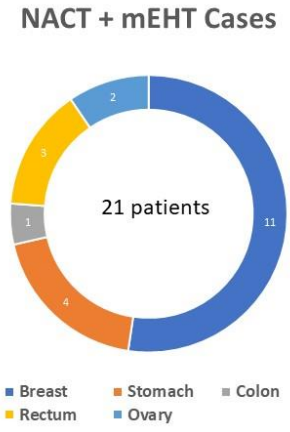
- 203 patients
- Age; 51 ± 9 yrs
- Sex; male, 148 *vs* female 53
- 101 breast, 26 stomach, 13 thyroid, 12 colon, 10 rectum, 9 lung, 8 ovary, 6 liver, 5 cervix, 5 sarcoma, 5 pancreas and 3 oesophageal cancer

NACT + mEHT

- 21 patients
- Age; 48 ± 6 yrs
- Sex; male, 16 *vs* female 5
- 11 breast, 4 rectum, 3 stomach, 2 ovary and 1 colon cancer

오아시스 요양병원 닥터 오아시스





오아시스 요양병원 닥터 오아시스

Concurrent Treatment

Types	Chemotherapy	Radiation Therapy	Condition
Breast	AC[1], DC[2], DCF[3]	No	≥5cm, invading into skin/chest wall, axillary lymph nodes(+)
Rectum	CAPEOX[4], FOLFOX[5]	Yes	T staging, location
Stomach	XELOX[6], FOLFOX	No	Mesentery, para-aortic lymph node , major vessel involvements, surrounding organs
Ovary	CT[7], CTB[8]	No	Peritoneal carcinomatosis, Debulking surgery
Colon	FOLFOX	No	Pericolic adipose tissue(+), surrounding organs

AC[1];doxorubicin+cyclophosphamide, DC[2];docetaxel + cyclophosphamide, DCF[3]; docetaxel + cyclophosphamide+ 5-FU, CAPEOX[4];capecitabine+oxaliplatin, FOLFOX[5]; 5-FU+oxaliplatin,XELOX[6];capecitabine+oxaliplatin, CT[7];carboplatin+paclitaxel, CTB[8]; carboplatin+paclitaxel+bevacizumab

오아시스 요양병원 닥터 오아시스

Example; Breast Cancer Case

NACT + mEHT; pCR Case

- F/72; Jul, 2017 -, axillary lymph nodes(+) triple-negative left breast cancer, AC + docetaxel sequencing NACT

Stage (cT2cN1M0)

*MMG/Breast sono('17.6.15): 2.4x2.2x3.0 cm irregular mass in Lt 12h N7cm, Three borderline LNs in Lt Ax level I-II,
*o/s C-CT('17.6.23): Lt. breast cancer and mildly prominent axillary LNs, GB and far distal CBD stone.
*BS('17.6.28): NED
*PET('17.6.28): Lt. breast cancer, Possible metastatic LNs in the Lt. axilla level I
-->LA breast ca, cT2N1M0, IIB로 preOP AC#4 (17.7.5-17.9.13)
#4후 C-CT(17.9.14): Much decreased size of left breast cancer and ipsilateral axillary LNs
-->docetaxel #4 (17.10.11-17.12.15)

Breast, left, "12H", needle biopsy:
INVASIVE DUCTAL CARCINOMA with
1) nuclear grade: 3/3
2) histologic grade: III/III
3) DCIS component: not identified
4) maximum diameter of invasive carcinoma: 11 mm
IHC :
- Estrogen Receptor : Negative
- Progesterone Receptor : Negative
- P53 : Positive in >75%
- Her-2 : Negative (-/3)
- Ki-67 :Positive in 30%

SNUH Pathology Report

오아시스 요양병원

Surgical Pathology Findings

2018.1.12 BCS+ SLNB, lt (post NCT): ypT0, ypN0/4 pCR

2018.1.12 BCS+ SLNB, lt (post NCT)
postop 1st visit

path : Breast, left, breast conserving surgery:
NO RESIDUAL TUMOR (see note2)
- Post-neoadjuvant chemotherapy status
- Previous pathology report: S 17-32578 (INVASIVE DUCTAL CARCINOMA)
- Microcalcification: absent
- Lymphatic emboli: absent
- Vascular emboli: absent
- Surgical margins:
  superior margin: clear
  inferior margin: clear
  medial margin: clear
  lateral margin: clear
  superficial margin: clear
  deep margin: clear
- Number of metastatic lymph nodes: 0
- Number of examined lymph nodes: 4
  (sentinel LN#1-#2, 0/4 (Fro#1-2); "Lt. axillary tissue", 0/0)

SNUH Pathology Report

오아시스 요양병원

NACT + mEHT; Efficacy*

Types(No)	complete remission	partial remission	stable disease	progressive disease
Breast(10)	2	5	3	0
Rectum(4)	0	4	0	0
Stomach(3)	0	1	2	0
Ovary(2)	0	2	0	0
Colon(1)	0	1	0	0

by *RECIST 1.1

오아시스 요양병원

NACT + mEHT; TEAE*

- Tolerable TEAE
- Different type of toxicities depend on chemotherapy protocols
- No grade 3 or higher non-hematologic toxicities**
- Mild mEHT-related toxicities less than grade 2
  - Blister, pain, erythema, general weakness
  - Chest discomfort due to pressure in breast cancer patients

*TEAE; treatment-emergent adverse event
** National Cancer Institute Common Toxicity Criteria, 3.0 v

오아시스 요양병원

NACT + mEHT; Conclusions

- Breast, rectal cancer; majority
- High intention to surgery rate
- Tolerable TEAE as similar as when doing conventional NACT
- May reduce local recurrences and early micrometastasis
- Future data collecting with other mEHT using hospitals for further clinical study in academic hospitals

오아시스 요양병원

Thank you

감사합니다.

mEHT - Results on CA - Esterioneuroblastoma - Brazilian Experience

Shirley Pontes[1], Francisco Azevedo[2]

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Presented at the 37th ICHS, Thessaloniki

Cite this article as:

Pontes S., Azvedo F. (2019): Effectiveness Clinical Case Report
mEHT - Results on CA - Esterioneuroblastoma - Brazilian Experience, Oncothermia Journal 27: 76- 87
www.oncotherm.com/sites/oncotherm/files/2019-10/mEHT_Results_on_CA.pdf

Cancer incidence in Brazil is as high as in developed countries. The Brazilian Unified Health System (SUS), which provides health care to the majority of the population, offers conventional oncology treatments such as chemotherapy, radiotherapy, hormonal suppressors and surgery. The possibility to offer modulated electro-hyperthermia (mEHT) is not yet being considered by the Government. There is, nevertheless, a growing number of cancer patients interested in the benefits of mEHT. Some of them, after being treated with traditional methods, see new hope in mEHT. Others see it as a complementary treatment. This report does not intend to provide scientific data, but rather a clinical contribution.

Aim

Our aim is to present a case study, showing a brief patient history, the evolution of malignancy despite conventional treatments (chemotherapy, radiotherapy and immunotherapy) and the results with mEHT as well as support therapies. Conventional treatments were undertaken from 2015 to 2017 but were interrupted at the end of 2017 due to high toxicity. The treatment with mEHT and support therapies were provided from January to April/2018.

Development

The patient is a white skin, 47 years old male, diagnosed in 2014 by biopsy with Esthesioneuroblastoma (CID 10 C30). The clinical assessment at the beginning of the treatment with mEHT was: important edema on the left side of the face, severe convergent strabismus in the left eye, duplicated vision; patient reporting sedentary lifestyle, unrestricted feeding, insomnia, feeling depressive, discouraged, unable to work and drive, suffering sequel from previous and recent treatments, and weight loss of 20 kilos.

Protocol

mEHT -130 W/ 60min 3 times a week, a total of 36 sessions; no chemotherapy or radiotherapy; oxygen therapy by Manfred Von Ardenne, galvanic micro-current, pulsed magnetotherapy field, Rife frequency therapy (36 session - 20 min), endovenous supplementation of minerals, vitamins, amino acids (500 ml X 12 session) and curcumin supplementation (SC 24 X 200 mcg, 2 ml), ozone therapy rectal 2 X week, reduced intake of simple carbohydrates, Joanna Budwig diet, homeopathic support, and "a more healthy lifestyle".
RESULTS: on Pet scan dated April/2018 and the oncological evaluation confirms the total remission of the Esthesioneuroblastoma and cervical lymph nodes, total remission of the facial edema, and 90% strabism recuction. The clinical impressions show significant improvement of energy and quality of life, and great improvement of vision. Still remains a slight strabismus, to be analyzed by the ophthalmologist. The patient continues with a low carb diet. He is able to drive safely and returned to normal work activities. Suggested oncological follow-up every six months.

mEHT- Clinical Case Report Results on CA – EsterioNeuroblastoma - Brazilian Experience

MD - Dr. Francisco Humberto F. Azevedo
MSC Shirley Pontes
Brasilia , BRASIL
20/ Sept/ 2019

Instituto de MEDICINA BIOLÓGICA

mEHT- in Brazil Cancer Treatment

Instituto de MEDICINA BIOLÓGICA

MD Dr. Francisco Humberto F. Azevedo

43 year MD (Surgeon + Homeopatic + Nutrologist) since the last 20 years he is using Integrative therapies on treatments

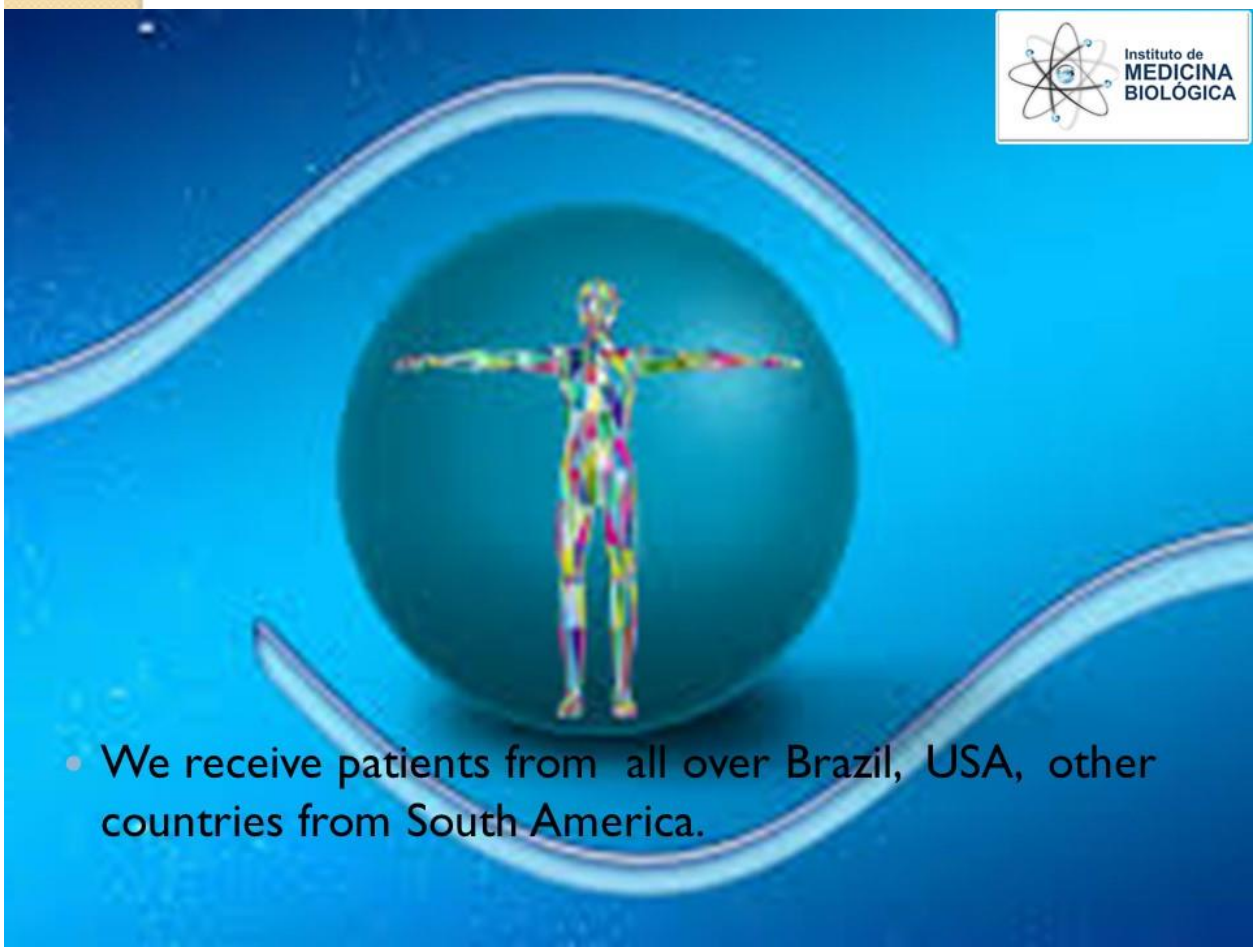
Shirley Pontes – Gerontologist

Master in Prostate Cancer toxicity of RT, QT, Hormone therapy and PR radical

Fitoterapist + Integrative therapies

mEHT against Cancer in Brazil

- First EHY2000 imported in Brazil - 2012;
- Treatments since 2013;
- mEHT is considered as a complementary treatment;
- There is no legislation about it.
- Legislation: Still in process of Register
- We are against the "Main Stream power"
- FDA – USA inspires legislation to ANVISA- Brazilian Regulation Agency



- We receive patients from all over Brazil, USA, other countries from South America.

The Cancer in Brazil

Brazilian statistics are equivalents as international leading:

- The statistics increases proportionally to the population.
- The Brazilian Unified Health System/SUS offers free public services treatments based on traditional oncololy:
  - Chemotherapy, Radiotherapy, Surgery and hormonal suppressors.
- **Immunotherapy** is not recognized as a treatment yet, in Brazil
- mEHT is not authorized as a Cancer treatment yet, in Brazil

The Brazilian Government did not consider yet the possibility to offer mEHT to population.

For a while, the patients from public health service in Brazil - will be treated by the "main stream"- they hve no other chioice.

The Main Stream is a Great Business

They believe in statistical significance

Another stream is rising up in Brazil
... and in the world!

Profile of Brazilian patients on IMBiologica

- 82% between 40 e 70 years
- 68% female
- 87% polithreated patients

  (Chemoterapy, Radiotherapy, Hormonal supression, Surgery, and Immunotherapy)
- 43% terminal patients
- 5% first cancer treatment: They refuses the traditional treatments.

AIM - Case Report

- Patients with **CA EsterioNeuroblastoma** treated with mEHT and supportive therapies.
- Patient historical evolution of malignancy during treatment with traditional oncology.
- Present images and results with mEHT treatment and other support therapies used.

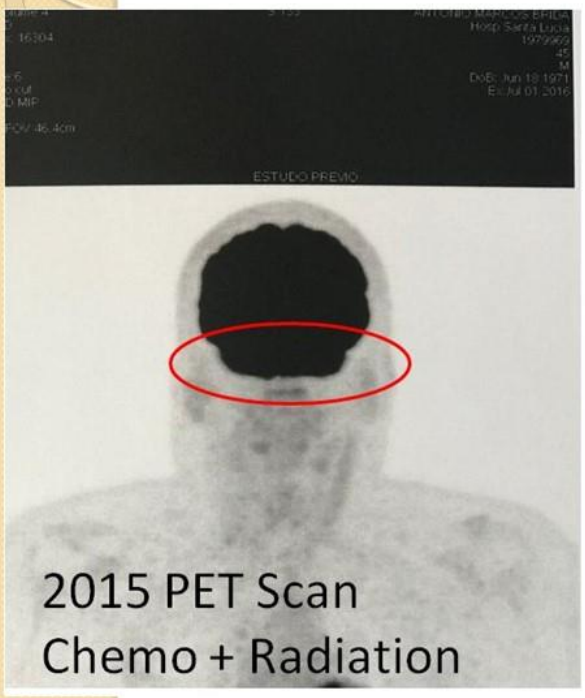
It does not intended to offer scientific data, but rather a clinical report.

Patient Profile

M. Brida: Male, White skin, 47 years old

- 2014 diagnosed C30- CA EsterioNeuroblastoma
- 4 years treating by traditional methods.
- Polytreated patient
  - CT, RT, and 3 sections of Immunotherapy
- Hopeless, he begins mEHT as a last possibility.

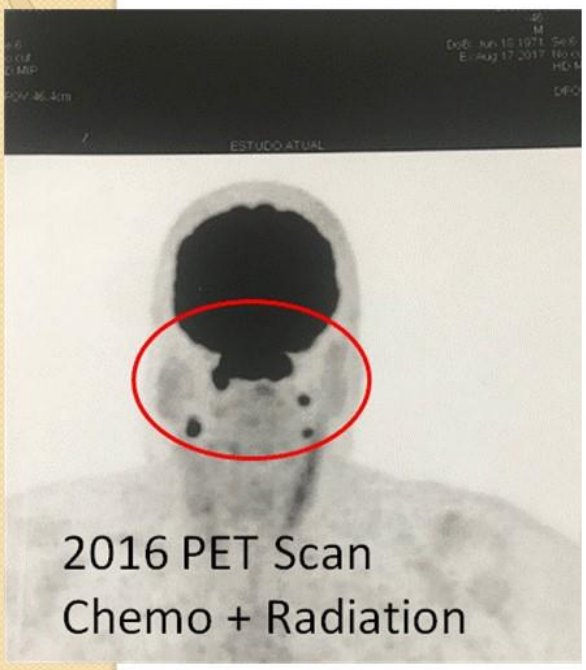
M.Brida:
Male, White skin, 47 years old



2014 diagnosis

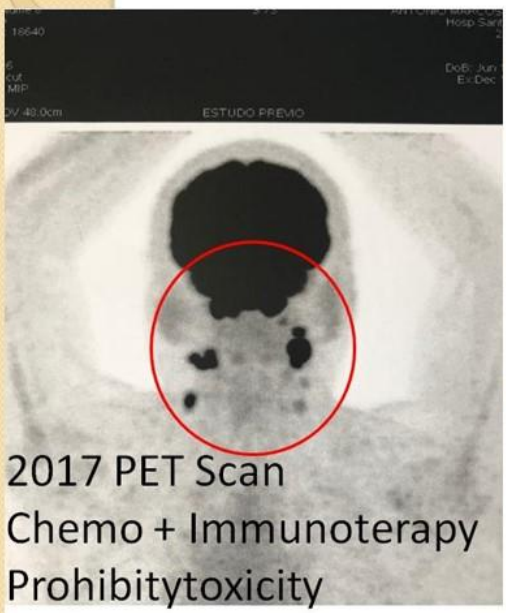
2015 - Patient was treated with Chemo and Radiotherapy.

M.Brida:
Male, White skin, 47 years old



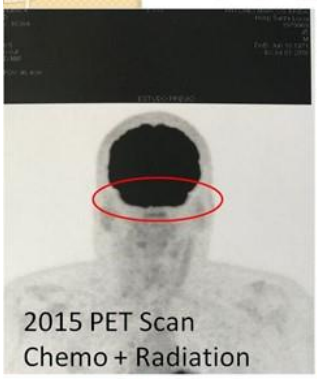
- 2016 - Identified the expansion of malignant cells to neck lymphonodes.
- In expansion

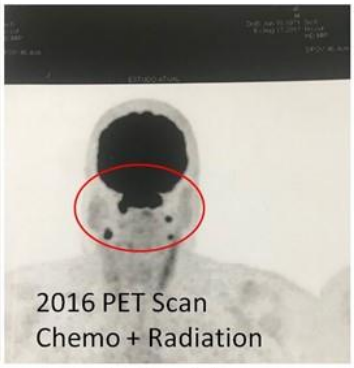
M. Brida:
Male, White skin, 47 years old



- 2017- Expansion of malignant,
- Treated with stronger QT which has caused rejection.
- The MD decided for Immunotherapy;
- Due hard toxicity, the MD decided to interrupt the treatment, after third section.

M Brida


2015 PET Scan
Chemo + Radiation


2016 PET Scan
Chemo + Radiation


2017 PET Scan
Chemo + Immunoterapy
Prohibitytoxicity

???

- Swollen face on left side.
- Convergent view (Strabic), Double vision.
- Depleted immunity, Depressed, unmotivated, social isolation.
- Unable to work, suffering sequel from previous treatments.
- Weight loss of 20 kilos.
- Denial: Smoking, alcoholism.
- Confirms: insomnia, sedentary, unrestricted feeding.

2018 - Phase 3: mEHT + IMB integrative program from January to April 2018.

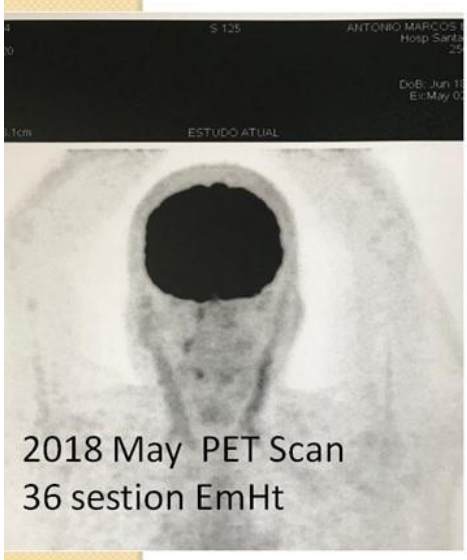
- Diet: Reduced intake of simple carbohydrates, Dra. Joana Budwig, Gerson therapy; Reduce inflamation, increase funcionalities;
- Medium size bolus electrode applied on the face- left side.
- eMHT 3 X week 120W/ 60min. 12 sessions/monthly X 3 months
- Homeopatc support.
- Suggested "Health life stile" ;
- Oxygen therapy by Manfred Von Ardene (36 session - 20 min), Galvanic micro current (36 session - 20 min); Magneto therapy (36 session 20 min), Rife frequency (36 session 20 min)
- Ozoneted blood therapy+ Endovenose supplementation (vitamins, minerals, amino acids) + VIT D3+ Curcumin + DCA + CBD.
- O3 Rectal 3 X week + other detox and eletrotheraopies;

Phase 3: mEHT + IMB Integrative Program

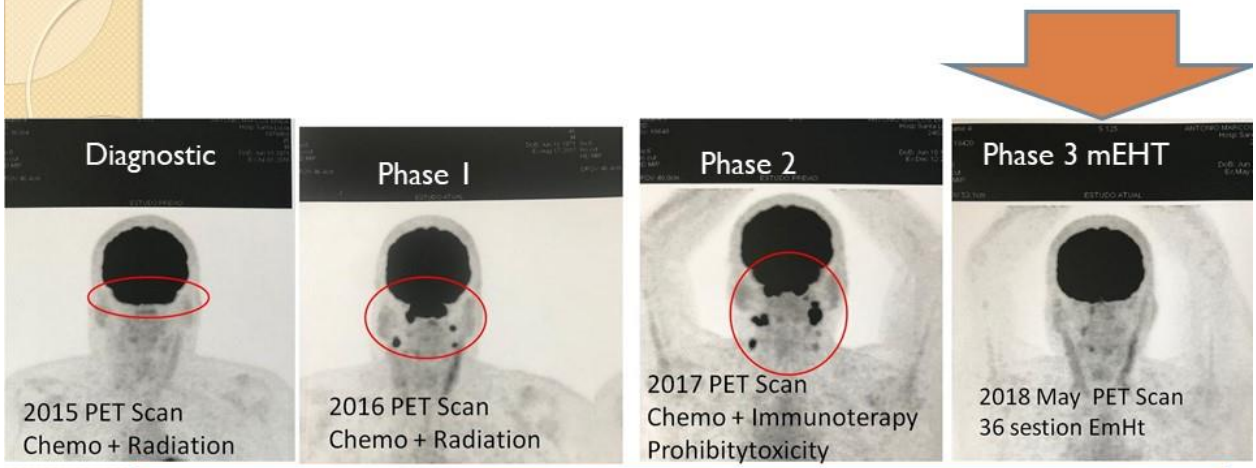
After 36 session of mEHT, shows the clinical impression:

- 100% reduction of facial edema,
- 80% reduction of strabism.

PETscan Dez/17 X PETscan May /18



"Resolution of hypermetabolism on nasopharyngeal lesion in the inferior turbinate medial wall of the left maxillary sinus and bilateral cervical lymphonodes."



- The patient continues with dietary habits and also with follow-up with traditional oncology.
- The ophthalmologist suggests a surgical intervention to adjust the remaining strabismus.
- Follow-up every six months with IMBiologica.
- Until now .... he is doing good!

Thanks Professors… You are building great knowledge!

We are facing the patient , trying to transform the research results in

Reality..

Health …

Happiness …

for patients and his families!

Effectiveness of hyperthermia in clinical stage IV pancreatic cancer

Eiji Ono, Masatugu Yano,Takafumi Ohshiro, Masayuki Shishida, Daisuke Sumitani,Yuzou Okamoto, Makoto Och

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Presented at the 37th ICHS, Thessaloniki

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Ono E. et al. (2019): Effectiveness of hyperthermia in clinical stage Ⅳ pancreatic cancer, Oncothermia Journal 27: 88- 93
www.oncotherm.com/sites/oncotherm/files/2019-10/Effectiveness_of_hyperthermia.pdf

Although recent progress of chemotherapy for the pancreatic cancer provide improvement of the patients' prognosis, the advanced pancreatic cancer patients in clinical stage IV is still quite difficult to increase the survival rate. Hyperthermia is expected as an effective treatment for such patients in combination with chemotherapy. In order to investigate the effectiveness of hyperthermia using Thermotoron RF-8 combined with chemotherapy for clinical stage IV patients we examined the outcome of the patients in the periods until two years from the beginning of this therapy. The results were compared to the registered data of the multi-center of Japan in the patients of stage IV treated with chemotherapy alone. The aim of this study is to investigate whether hyperthermia contribute to improve the outcome of the pancreatic cancer patients in clinical stage IV.

Material/Methods
28 patients with advanced pancreatic cancer in clinical stage IV treated by more than 5 times of hyperthermia were examined. These patients had distant metastasis or peritoneal dissemination and were treated with several types of combination chemotherapy. Among them, 9 patients had the history of surgery for the primary tumour and 21 had no surgery. Hyperthermia using the Thermotron RF-8 heating device was administrated for 50 min each time just after chemotherapy 3 or 4 times in a month. The evaluation of outcome of the patients was expressed as CR, PR, SD, PD and overall survival. This evaluation was done at 3, 6, 12, 18 and 24 months after the beginning of this therapy.

Results
In the response to the treatment at 3 months, CR was 0 %, PR was 18%, SD was 39% and PD was 42%. Survival rate was 97%. At 6 months, CR was 0 %, PR was 16%, SD was 24% and PD was 40%. Survival rate was 80%. At 12 months, CR was 6%, PR was 0%, SD was 6% and PD was 59%. Survival rate was 41%. At 18 months, CR was 6%, PR was 0%, SD was 0% and PD was 19%. Survival rate was 25%. 2 patients survived more than 2 years. Among 12 patients observed for these two years, two patients survived, and one patient is still in the state of CR. The survival rate in 2 years was 17%. According to the Japanese Association of Clinical Cancer Centers, in the registered data in 2010, 1-year survival rate and 2 years survival rate of the stage IV pancreas cancer patients treated with chemotherapy alone, is 20% and 8% respectively. Although the number of the patients in our hospital is small, the outcome of them were superior to that of the registered patients in the Japanese Association of Clinical Cancer Centers, who were treated without hyperthermia.
Conclusion: The results in this study indicate that the treatment of hyperthermia combined with chemotherapy have a possibility to contribute to prolong the survival of the patients even in the clinical stage IV.

Introduction
In spite of the recent progress of the chemotherapy for the pancreatic cancer patients provide improvement of the patients' prognosis, the advanced pancreatic cancer in clinical stage IV with local recurrence, distant metastasis or peritoneal dissemination is still quite difficult to increase the survival rate. Hyperthermia is expected as an effective treatment for such patients in combination with chemotherapy (1,2,3). During 3 years and 5 months since 2016, 41 pancreatic cancer patients in various situations were treated in our hospital with hyperthermia using Thermotron RF-8. In this study, we evaluated the result of 28 patients treated more than 5 times by this therapy. In order to investigate the effectiveness of the hyperthermia using Thermotron RF-8 combined with chemotherapy for the patients in clinical stage IV, including tumour recurrence after surgery. We examined the outcome of the patients in the periods until two years after the beginning of this therapy. The results were compared to the registered data of the multi-center of Japan of the pancreas cancer patients in Stage IV treated with chemotherapy alone. The aim of this study is to investigate whether hyperthermia contribute to improve the prognosis of the pancreatic cancer patients in clinical stage IV.

Material and Methods
28 patients (from 40 to 79 years of age) with advanced pancreatic cancer in clinical stage IV treated by more than 5 times of hyperthermia combined with chemotherapy were examined. 16 cases were male patients, 12 cases were female patients. These patients had distant metastasis or peritoneal dissemination

and were treated with the several types of combination chemotherapy, FOLFIRINOX, Gemsitabin plus nab-Pacritaxel or S-1. Among them, 9 patients had the history of surgery for the primary tumour and 21 had no surgery (Table 1).

Characteristics of the 28 patients

Gender	
Male	16
Female	12
Age, years	
Median	64.3
Range	40-79
Metastic state	
Liver	18
Lung	7
Peritoneum	8
Pancreatic resection	
No	20
Yes	8

Heating device of Thermotron RF-8, which is widely used in Japan, was used for the hyperthermia treatment. Patients were administrated for 50 min each time just after chemotherapy 3 or 4 times a month. Most of the patients had the medical history of treatment, including surgery or standard chemotherapy in the other hospital before starting our therapy. Evaluation of outcomes of the patients was expressed as complete remission (CR), partial response (PR), stable disease (SD), progress disease (PD) and survival rate. This evaluation was done at 3, 6, 12, 18 and 24 months after the beginning of this therapy.

Results

In the response to the treatment at 3 months, CR was 0 %, PR was 18%, SD was 39% and PD was 42%. At 6 months, CR was 0 %, PR was 21%, SD was 24% and PD was 28%. At 12 months, CR was 6%, PR was 0%, SD was 6% and PD was 59%. At 18 months, CR was 6%, PR was 0%, SD was 0% and PD was 19% (fig 1).

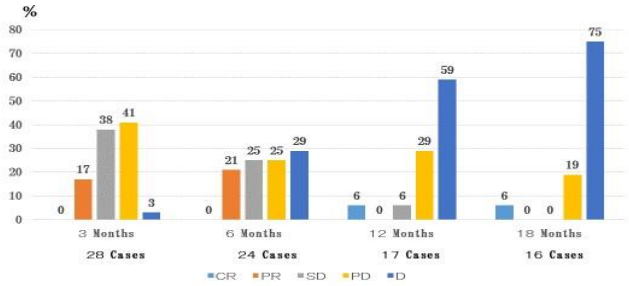

Figure 1: Outcomes were evaluated in 3, 6, 12 and 18 months after the beginning of hyperthermia therapy. Each number indicated the percentage of the patients in the same periods.

The outcome is getting worse, but at 6 months nearly 50% of the patients were keeping PR or SD, and at one year 41 % was still alive. Up to now, we observed 12 patients for more than two years. Among them, two patients were alive, and one of them is still in the state of CR. The survival rate of 1 year and 2 years were 41**%** and 15% respectively. According to the registered data in 2010 of Japanese Association of Clinical Cancer Centers, 1-year survival rate and 2 years survival rate of the stage Ⅳ pancreatic cancer patients treated with chemotherapy alone is 22.7 % and 6.1 % respectively (Fig 2).

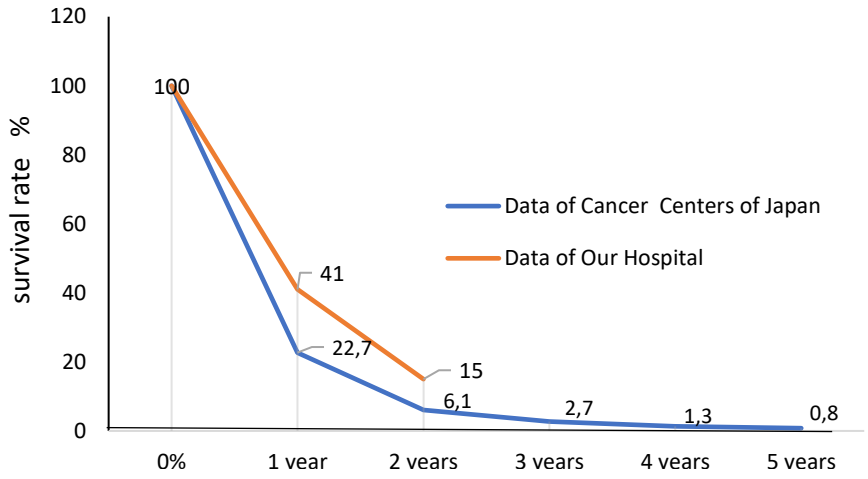

Figure 2: Survival rate until two years in our cases, and that of Japanese Association of Clinical Cancer Centers, (total 70 centers).

Even though the number of the patients in our study is small, the outcome of the patients were superior to that of the registered patients in Japanese Association of Clinical Cancer Centers, who were treated without hyperthermia. In our study, 3 cases showed the quite good response to this therapy.

First case

58 years old male patient. Diagnosis is invasive pancreas ductal carcinoma in the pancreas head with multiple liver metastasis. Chemotherapy was administered using the regimen of GEM + nabPTX by every 4 weeks for 2 years. Hyperthermia was started two months after the beginning of the chemotherapy. It was done on the same day after the chemotherapy. Before treatment, low density tumour was located close to the duodenum. After 1 year, the primary tumour disappeared, and after 2 years, the head of the pancreas was still tumour free. Liver metastasis was observed before the treatment, but 1 year later, those disappeared, and 2 years later the patient is still tumour free. Before the treatment, the CA19-9a tumour marker level was quite high; it was 26,494 unit/ml. But 3months after starting hyperthermia, the tumour markers (CEA, CA19-9) decreased within normal level. This situation continued at 2 years after starting this therapy. These results indicated that this patient is in clinical CR (Fig 3).

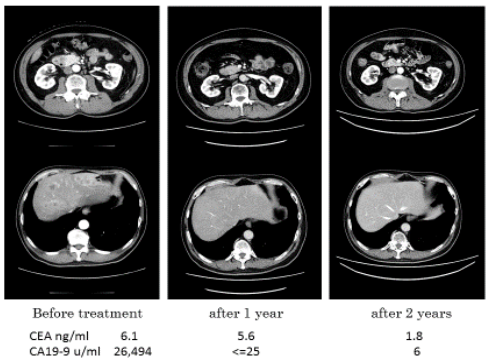

Figure 3: CT findings of the pancreas, liver and the tumour marker for two years in case 1

Second Case

The second case is a 65 years old male patient. The diagnosis is pancreatic cancer in the body to tail, with multiple liver metastasis. For the first chemotherapy, the regimen of GEM + nabPTX was administrated every 4 weeks and was continued for four months. After that, regimen was changed to GEM + S1. It was administrated every 3 weeks. This regimen is still continued until now. Hyperthermia was started at the same time as chemotherapy. The treatment was performed on the same day just after the chemotherapy. In the CT

findings, multiple liver metastasis and primary tumour is located in the pancreas body to tail as a low-density lesion before the treatment. In contrast,7 months later, metastatic tumour in the liver is markedly contracted. The primary tumour could not be detected. The level of tumour marker before the treatment, especially the level of CA19-9 was extraordinarily high, 551,790 U/ml, but 7 months after starting the hyperthermia, it decreased to 6,257. Therefore, the situation of this patient is considered to be PR (Fig 4).

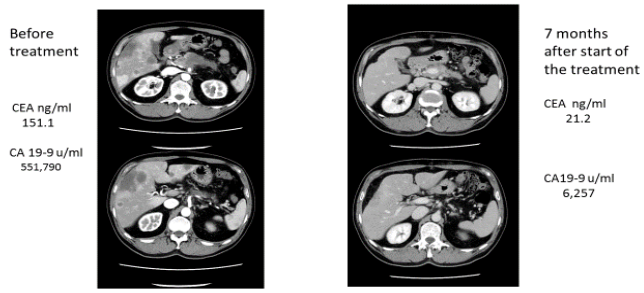

Figure 4: CT findings and the level of tumour marker before treatment and 7 months after the start of the treatment.

We estimated the temperature in the stomach during hyperthermia in this patient, using gastric catheter inserted sensor of temperature. The power of the radiofrequency for this patient was maintained about 1200 W. The maximal temperature was just over 44℃ by prone position.

Third Case:

58 years old male patient. The diagnosis is pancreatic cancer in the tail with invasion to the spleen and kidney with multiple liver metastasis. For the chemotherapy, the regimen of FOLFIRINOX was done during the first 3 months, after that it changed to GEM + nabPTX, and continued until now. FOLFIRINOX was done every 4 weeks for 3 months, GEM + S1 was done every 4 weeks. Hyperthermia was started at 2 months after the beginning of the chemotherapy. Treatment was done on the same day after the chemotherapy. In the CT findings, a big tumour was located in the tail of pancreas invading into the spleen and metastatic liver tumour was observed. 5 months after starting the therapy, the tumour was reduced and also the metastatic liver tumour was contracted. The tumour markers (CEA, CA19-9) were decreasing gradually during 6 months after starting hyperthermia. These findings indicate that this patient is also in the situation of PR (Fig 5).

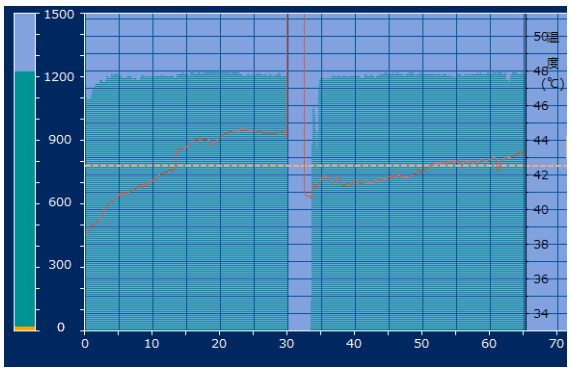

Figure 5: The record of estimation of temperature in the stomach during hyperthermia. Left axis is the power of RF (watt). Light green area indicates the change of the level of RF. Right axis is the temperature (℃). Horizontal shaft is time (min). Red line is the change of the temperature.

Discussion

It is generally important to decide the diagnosis in the early stage to provide good prognosis for malignant disease. Many cases of pancreatic cancer do not have the subjective symptoms in the early stage; therefore, patients do not always have a chance to receive surgery. According to the data of pancreatic cancer registry in Japan, respectable pancreatic cancer in the early stage account only 10% of all cases (4). The patients with no indication for surgery or recurrent cases after surgery are mainly treated with chemotherapy.

The regimen of the chemotherapy is on the way of progression (5,6), however it is still in the poor prognosis of the highly advanced cancer of stage IV, which have distant metastasis or peritoneal dissemination. Vascularity in the lesion of pancreatic cancer is relatively low in comparison with the other malignant tumour. That is one of the reasons why the effect of the treatment is limited, when the patients were treated with chemotherapy alone. Hyperthermia combined with chemotherapy is expected as an effective treatment for such patients to improve the outcome (7). In this treatment, the temperature of the target area is one of the important points to know the working situation of this treatment. It is not easy to estimate the temperature of the organ located in the deep part of the body directly. Pancreas is also quite difficult to do. We tried to estimate the temperature in the stomach during hyperthermia in a patient, using gastric catheter inserted sensor of temperature. Although this is not the temperature in the pancreas itself, it is considered to be nearly reflected the temperature of the deep area. In this case, the maximal temperature of the stomach was 43 to 44 ℃ during the treatment by RF power of 1200 Watt. These results were one of the evidences, which support the effectiveness of hyperthermia in this patient. The total outcome of our study is not yet satisfactory; however, the survival rate was improved in comparison with that of the registered data of the multi-center of Japan of pancreas cancer patients in stage IV treated with chemotherapy alone. Although the number of our cases were quite small to do the exact statistical analysis, the results indicated that hyperthermia treatment has a possibility to improve the prognosis even if in stage IV pancreatic cancer.

Conclusion

Hyperthermia treatment combined with chemotherapy have a strong possibility to contribute to prolong the survival of the patients even if in the clinical stage IV.

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Modulated electro-hyperthermia as palliative treatment for pancreatic cancer: a retrospective observational study on 106 patients

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Background
Pancreatic adenocarcinoma is one of the cancers with the poorest prognosis, resulting in a <10% survival rate at 5-years. Modulated electro- hyperthermia (mEHT) combines the heat-therapy with an electric field and has been increasingly used for cancer therapy alone or in combination with radiotherapy and chemotherapy. Clinical researchers show that hyperthermia is feasible not only for palliative care but has also therapeutic effects in pancreatic cancer.

Purpose
To monitor the efficacy and safety of mEHT for the treatment of pancreatic cancer.

Methods
We collected data retrospectively on 170 patients affected by stage III-IV pancreatic adenocarcinoma, and 106 were considered for this study. The sample was divided in two groups: patients that did not receive mEHT (no-MEHT) and patients that were treated with mEHT.
mEHT was performed using a capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (40-90 minutes). The applied power was 60-150 Watts. mEHT was performed in association with chemotherapy in 32 (82%) of patients whereas 7 (18%) received mEHT alone. The majority (54%) of no-mEHT group received a second line chemotherapy, whereas 31 (46%) did not receive any further treatment.

Results
106 consecutive patients were enrolled in this study, median age of the sample was 65 (range 31-80) years. After three months of therapy, tumor response in mEHT group was: partial response (PR) in 22 (56%) patients, stable disease (SD) in 15 (38%) patients and progression disease (PD) in 2 (5%) patients. Tumor response in no-mEHT group was: partial response (PR) in 4 (11%) patients, stable disease (SD) in 11 (31%) patients and progression disease (PD) in 21 (58%) patients.
The median overall survival (OS) of mEHT group was 17.23 (range 2.6-30.4) and 11,33 months (range 0.4-56.25) for non-mEHT group.

Conclusions
mEHT may improve tumor response and survival of pancreatic cancer patients.

Θεσσαλονίκη
Salonicco

Modulated electro-hyperthermia as Palliative treatment for Pancreatic cancer: a retrospective observational study on 106 patients.

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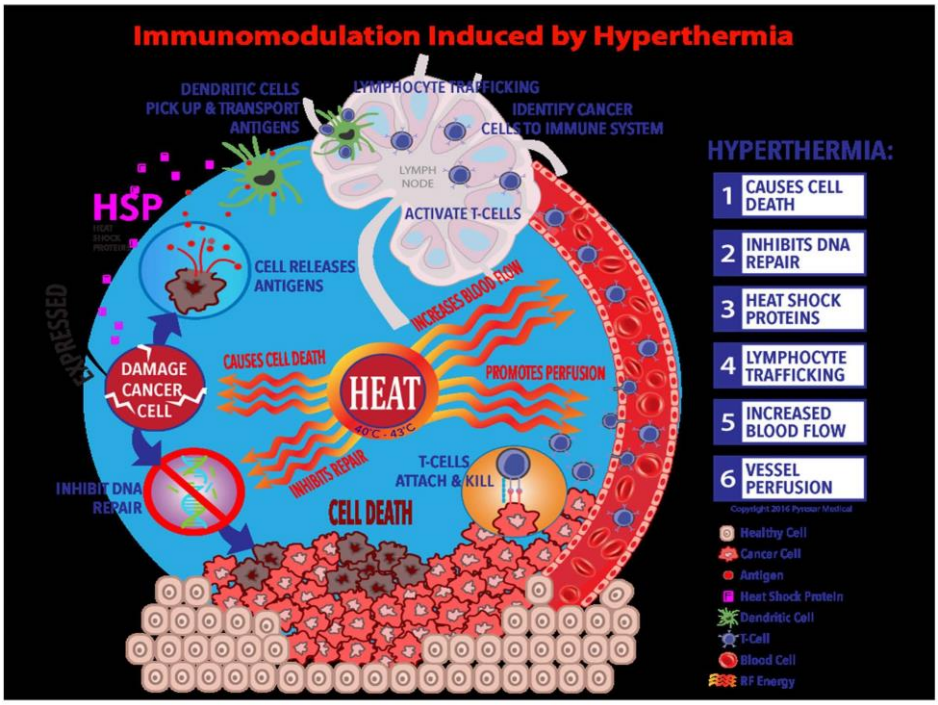


BACKGROUND

- Pancreatic adenocarcinoma has poor prognoses, resulting in a <10% survival rate at five years.
- Modulated electro-hyperthermia (mEHT) combines heat-therapy with an electric field and has been increasingly used for cancer therapy alone or in combination with radiotherapy and chemotherapy.
- Clinical research shows that hyperthermia is beneficial not only for palliative care but also has therapeutic effects in pancreatic cancer.

AIM

to motor the efficacy and safety of modulated electrohyperthermia (mEHT) for the treatment of Pancreatic cancer.

METHODS

- We collected data on 170 patients affected by stage III-IV pancreatic adenocarcinoma, and 106 were considered for this study.
- The sample was divided in two groups: patients that did not receive mEHT (no-mEHT) and patients that were treated with mEHT.
- mEHT was performed using a capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (40-90 minutes).
- The applied power was 60-150 Watts. mEHT was performed in association with chemotherapy in 32 (82%) of patients whereas 7 (18%) received mEHT alone.
- The majority (54%) of no-mEHT group received a second line chemotherapy, whereas 31 (46%) did not receive any further treatment.

Description of the sample

Ages	All patients		with mEHT		without mEHT	
	mean	median	mean	median	mean	median
average age (y)	64.5	65.3	61.8	62.6	66	67.8
Groups	All patients		with mEHT		without mEHT	
	n	%	n	%	n	%
males	59	55.7	24	61.5	38	56.7
females	47	44.3	15	38.5	29	43.3
non-metastatic	44	41.5	14	35.9	30	44.8
metastatic	62	58.5	25	64.1	37	55.2
site of metastases	All patients		with mEHT		without mEHT	
	n	%	n	%	n	%
liver	47	75.8	19	76.0	28	75.7
liver & elsewhere	4	6.5	4	16.0	0	0.0
lung	5	8.1	1	4.0	4	10.8
lymphnodes	2	3.2		0.0	2	5.4
peritoneum	1	1.6		0.0	1	2.7
bones	2	3.2		0.0	2	5.4
pelvis	1	1.6	1	4.0		0.0

Types of first line chemotherapy

type of first line CHT	All patients		with mEHT		without mEHT	
	n	%	n	%	n	%
gemcitabine oxaliplatin	49	46.2	14	35.9	35	52.2
gemcitabine	30	28.3	6	15.4	24	35.8
gemcitabine abraxane	8	7.5	5	12.8	3	4.5
gemcitabine FU	4	3.8	2	5.1	2	3.0
other	8	7.5	5	12.8	3	4.5
no	7	6.6	7	17.9	0	0.0

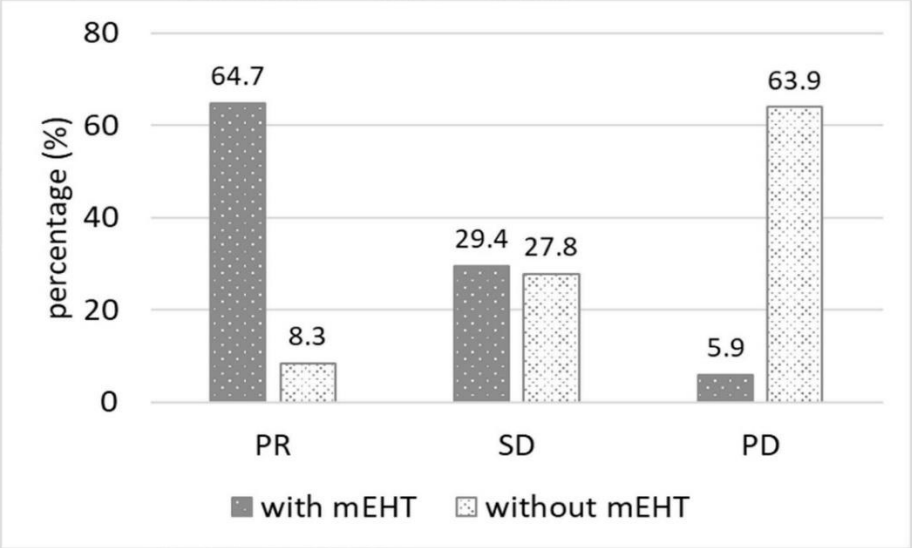
Types of second line chemotherapy

continuing of chemo	All patients		with mEHT		without mEHT	
	n	%	n	%	n	%
gemcitabine oxaliplatin	4	3.8	1	2.6	3	4.5
gemcitabine-carboplatin	3	2.8	0	0.0	3	4.5
gemcitabine abraxane	7	6.6	5	12.8	2	3.0
gemcitabine	31	29.2	23	59.0	8	11.9
folfiri or folfirinox	7	6.6	1	2.6	6	9.0
folfox	8	7.5	0	0.0	8	11.9
other	10	9.4	3	7.7	7	10.4
no	36	34.0	6	15.4	30	44.8

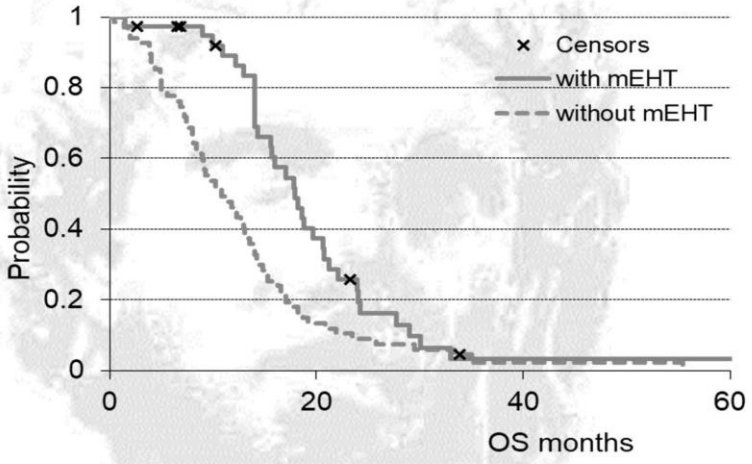
RESULTS

- 106 consecutive patients were enrolled in this study, median age of the sample was 65 (range 31-80) years.
- After three months of therapy, tumor response in mEHT group was: partial response (PR) in 22 (56%) patients, stable disease (SD) in 15 (38%) patients and progression disease (PD) in 2 (5%) patients.
- Tumor response in no-mEHT group was: partial response (PR) in 4 (11%) patients, stable disease (SD) in 11 (31%) patients and progression disease (PD) in 21 (58%) patients.
- The median overall survival (OS) of mEHT group was 17.23 (range 2.6-30.4) and 11,33 months (range 0.4-56.25) for non-mEHT group.

Tumor response at three months



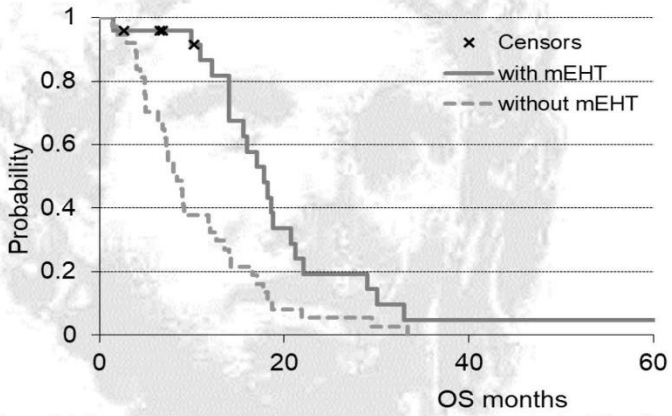
OS of the two study groups



p<0.00165

The solid line was the survival of mEHT group and the dashed line the non-mEHT. The x showed the censored patients.

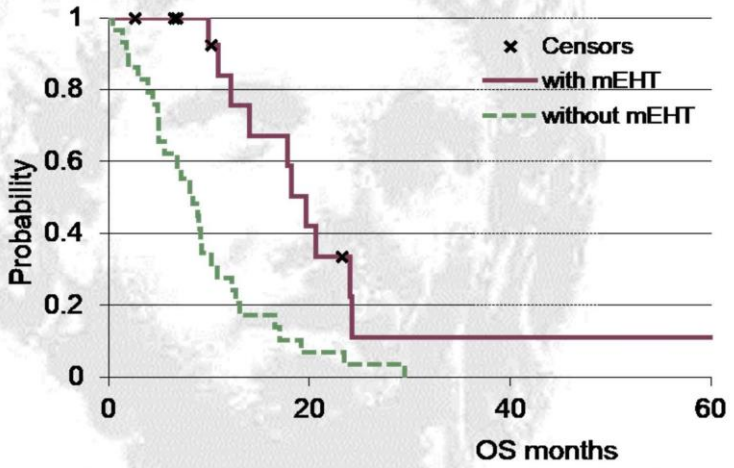
OS grouped by metastatic patients of the two groups of the study



p=0.0008

The solid line was the survival of mEHT group and the dashed line the non-mEHT. The x showed the censored patients.

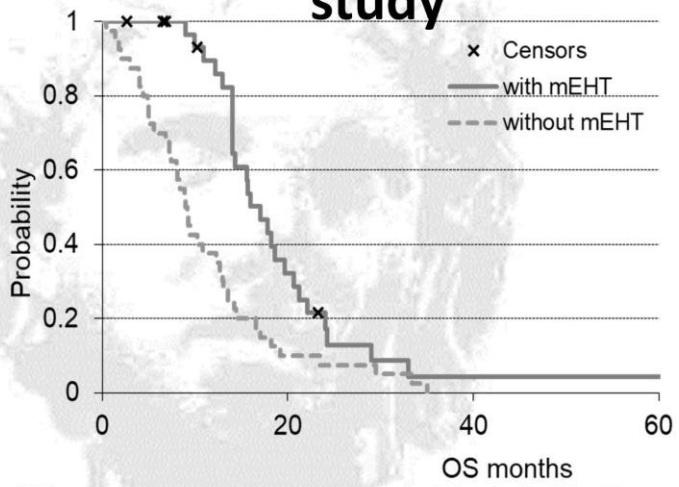
OS grouped by the first-line treatments of the study two groups



p=0.00047)

The solid line was the survival of mEHT group and the dashed line the non-mEHT. The x showed the censored patients.

OS grouped for non-resected patients of the two arm of the study



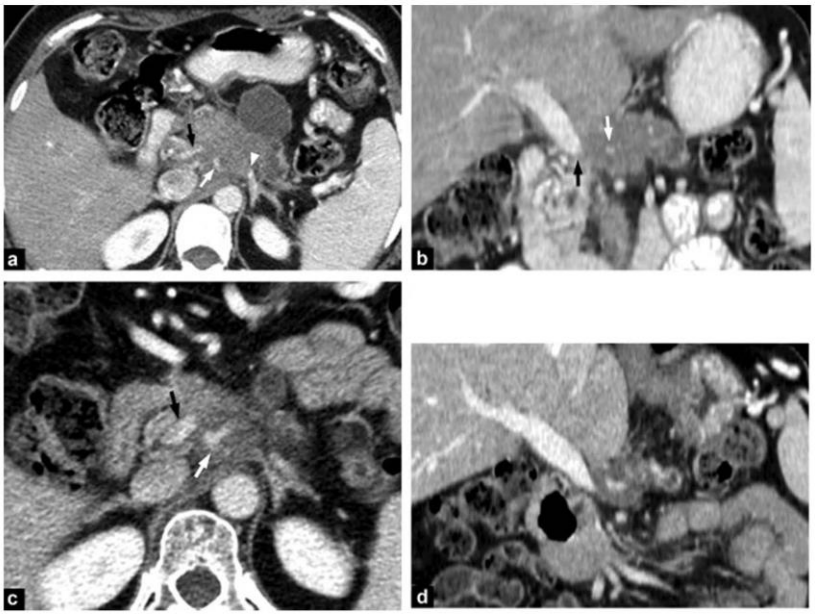
p=0.00094

The solid line was the survival of mEHT group and the dashed line the non-mEHT. The x showed the censored patients.

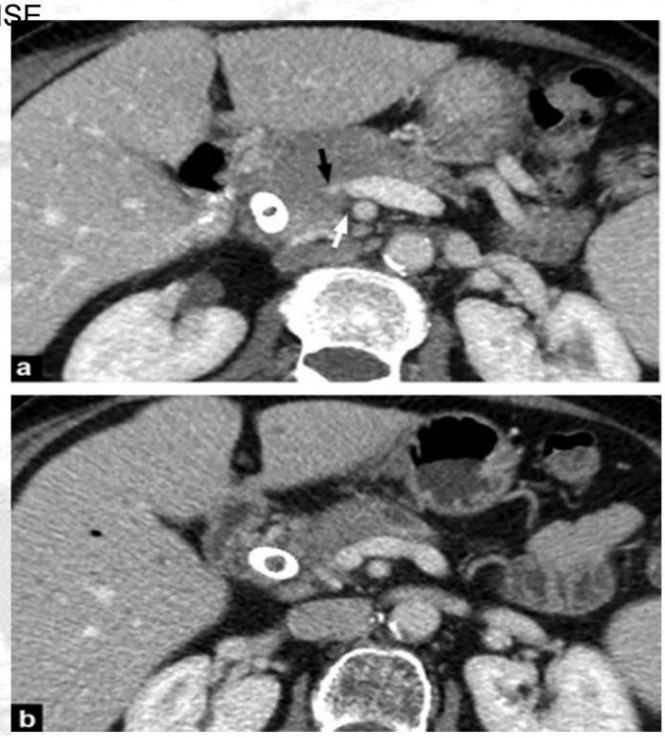
ADVERSE EFFECTS AND SAFETY

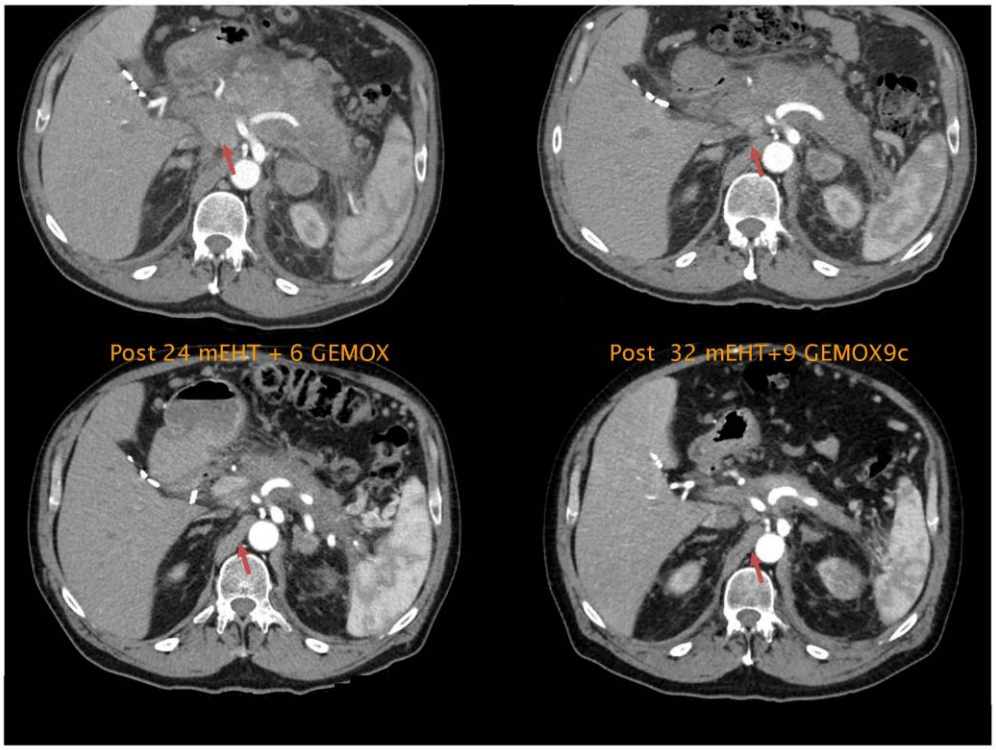
- Out of a total of 499 mEHT delivered sessions, the safety assessment of mEHT showed a limited number of adverse events 20/499 (4%).
- mEHT toxicity consisted of skin pain in 12 (2%) sessions and grade 1 burns in 6 (1%) patients and grade 2 burns in 2 patients.
- All these side effects were G1-G2 intensity and resolved with local medications and discontinuation of treatment for one week.

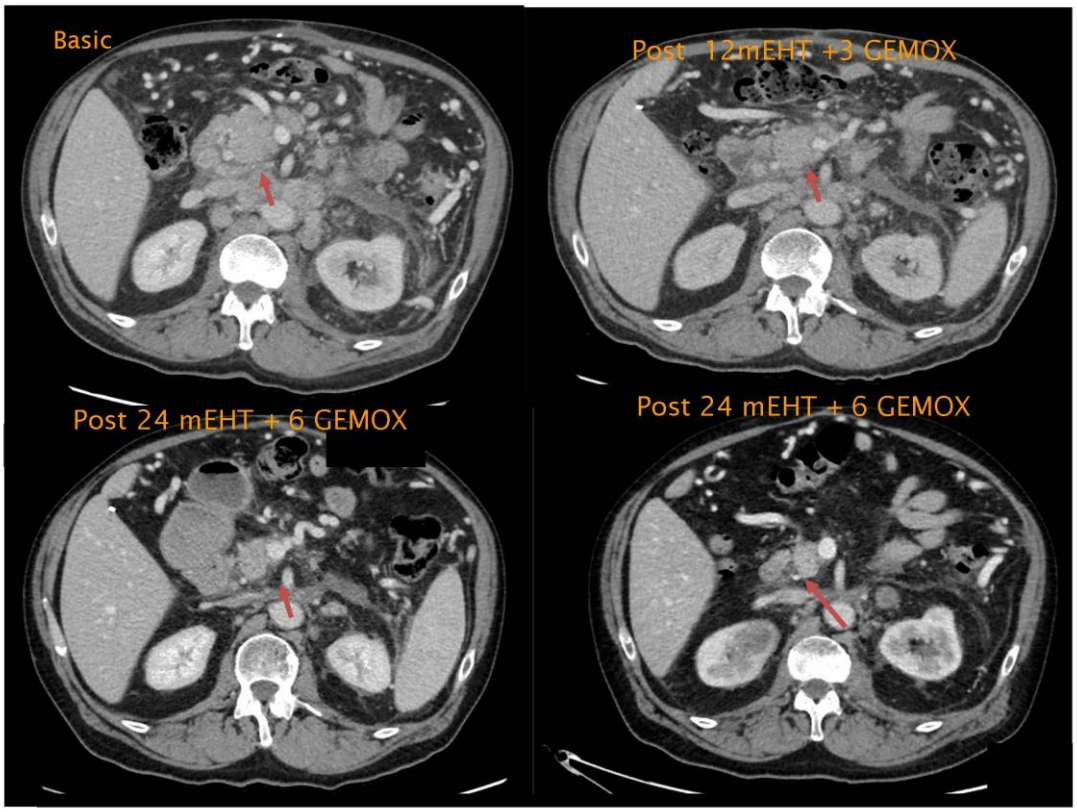
PT 26 - PANCREATIC CANCER (BODY) PROGRESSED AFTER 6 C. OF GEMOX, RESPONSE AFTER MEHT+ GEM (32 MEHT SESSIONS AND 8 C. OF GEM)

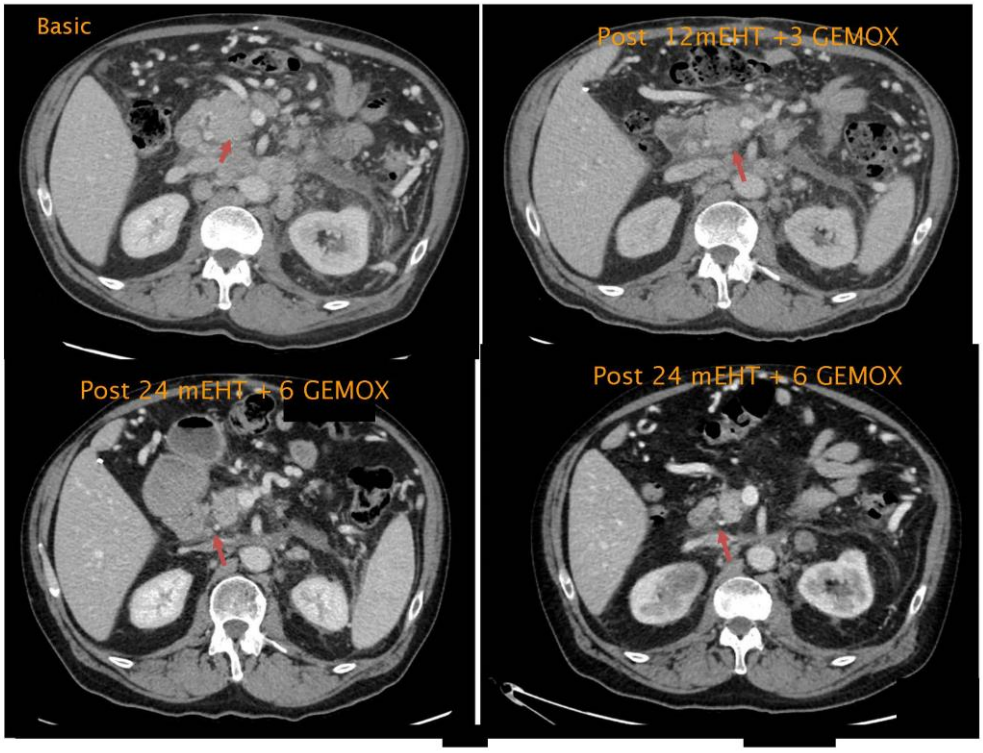


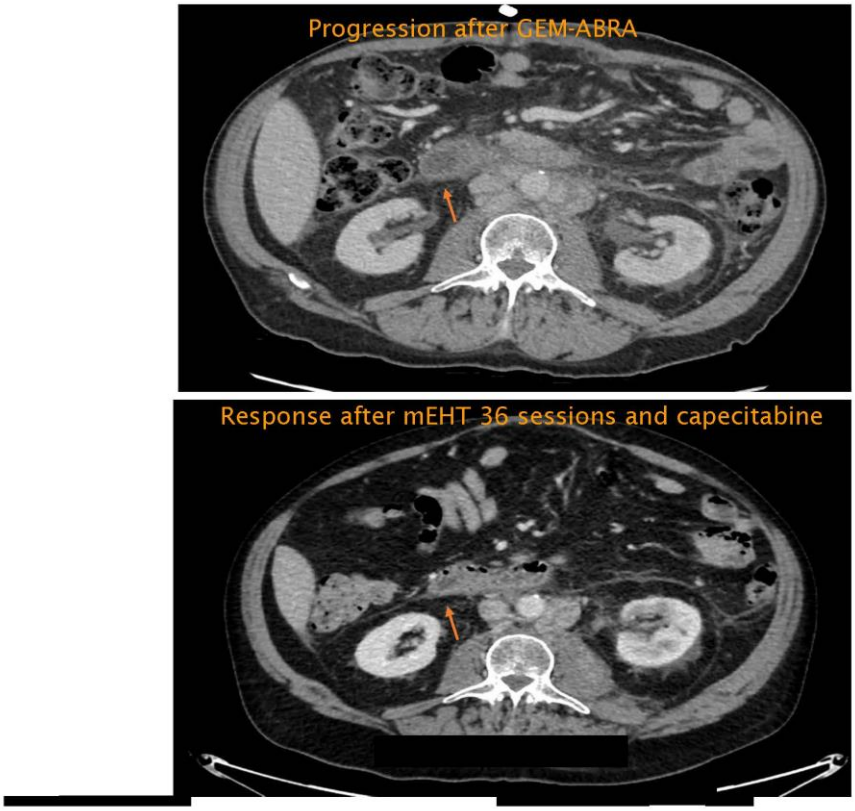
PT 33-PANCREATIC CANCER (HEAD) AFTER DRAINAGE RECEIVED MEHT (28 SESSIONS) PLUS GEM 9 C. SEE EVIDENCE OF RESPONSE

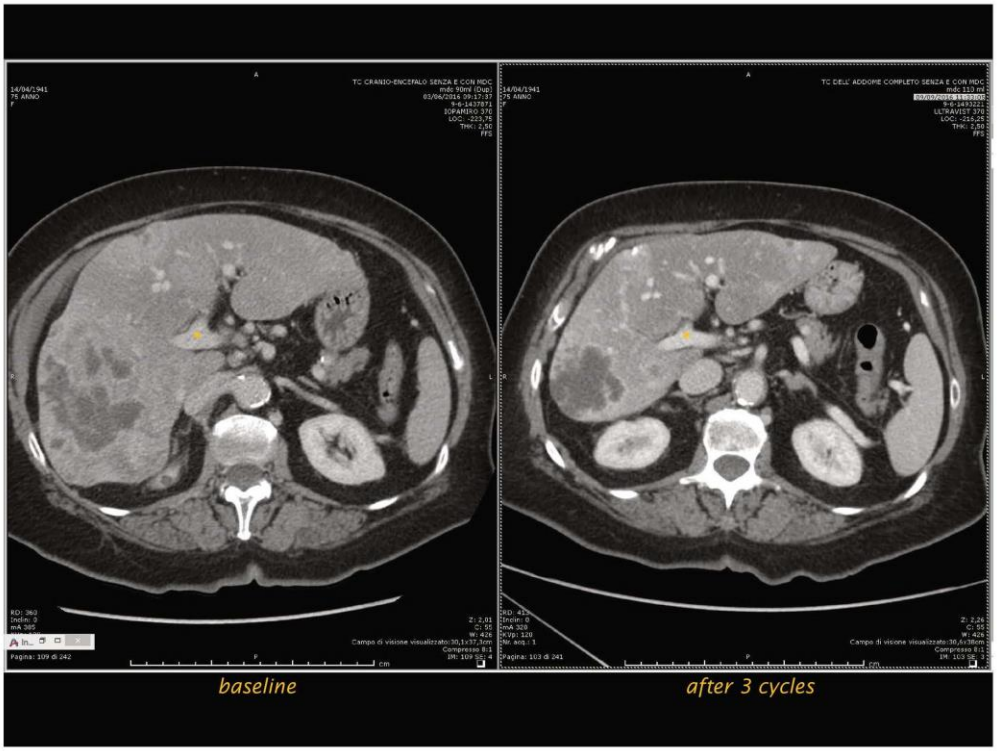



Post 24 mEHT + 6 GEMOX
Post 32 mEHT+9 GEMOX9c


Basic
Post 12mEHT +3 GEMOX
Post 24 mEHT + 6 GEMOX
Post 24 mEHT + 6 GEMOX


Basic
Post 12mEHT +3 GEMOX
Post 24 mEHT + 6 GEMOX
Post 24 mEHT + 6 GEMOX


Progression after GEM-ABRA
Response after mEHT 36 sessions and capecitabine



CONCLUSION

- Longer median OS and better tumor response were observed for mEHT group than for the control group.
- These results may suggest a beneficial effect of mEHT when combined with chemotherapy increasing response and OS for patients with locally advanced and metastatsic pancreatic cancer.
- The results of this study suggested also that mEHT could be safe for pancreatic cancer therapy, resulting in very limited side effects.
- Our data suggest to carry out further randomized trials

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Thank you

Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer

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To the memory of Melvin Cohn, founding fellow and professor emeritus of the Salk Institute for Biological Studies

Presented at the 37th ICHS, Thessaloniki

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www.oncotherm.com/sites/oncotherm/files/2019-10/Exploiting_autoimmunity.pdf

Introduction

As a result of the cancer immunotherapy revolution more than 2,000 immuno-oncology agents are currently being tested or in use to improve responses. Not unexpectedly, the 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for their development of cancer therapy by blockade of co-inhibitory signals. While success stories of terminal cancer patients achieving complete remissions are accumulating, not enough research has been done into the risks of the new therapies. Since the use of immunotherapy is becoming more common and is beginning to develop into first- and second-line treatments, autoimmunity is emerging as the nemesis of immunotherapy. Immune-related adverse events (irAEs) could affect any tissue; their incidence may reach up to 96% of patients; and toxicity is dose-dependent. While the combination of two immune checkpoint inhibitors (ICIs) increases efficacy, the incidence of severe adverse events is also increased. Apparently, ICIs cannot be restricted to the targeted anti-tumour T cell population. The long-lasting objective of cancer regression can only be achieved by paying a price: tolerance to healthy self-tissues is compromised.

Objectives, Material/Methods

In the face of an ipilimumab-induced pan-lymphocytic activation, a therapeutic paradigm shift is required. The task is not to desperately put the genie back in the bottle by immune suppressive treatments, but instead harnessing the autoimmune forces by an off label low-dose combined anti-CTLA-4 and anti-PD1 antibody blockade, which is supplemented with conventional interleukin-2 (IL-2) stimulation and hyperthermia.

Results

The proof-of-principle of the low-dose-combination therapy was demonstrated in a heavily pre-treated triple negative breast cancer (TNBC) patient with far advanced pulmonary metastases and severe shortness of breath, who had exhausted all conventional treatment. Her pulmonary metastases went into complete remission with transient WHO I-II diarrhoea and skin rash. She lived for 27 months after starting the low-dose-combination therapy. Since then, 111 stage IV cancer patients with a variety of cancer types have been treated. A retrospective analysis of these single cases demonstrated that the overall response (OR) rate was 48% with an objective response (ORR) of 33%, while irAEs of WHO grade I, II, III and IV were observed in 21%, 14%, 7% and 2% of patients, respectively.

Conclusion

Since the low-dose-combination protocol consists only of approved drugs and treatments, these single patient responses can be confirmed or refuted in prospective controlled clinical trials.

Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer
(Scand. J. Immunol. 2019 in press)

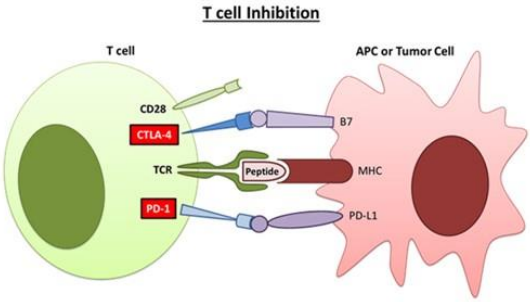
Tibor Bakacs, M.D., Ph.D., D.Sc, Ralph W. Moss, Ph.D., Ralf Kleef M.D.,
Marcell Szasz, M.D.,Ph.D., Colin C Anderson, Ph.D.

To the memory of Melvin Cohn, founding fellow and professor emeritus of the Salk Institute for Biological Studies

Highlights

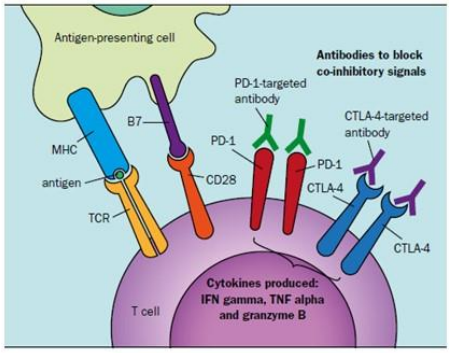
- Autoimmunity emerging as the nemesis of immunotherapy;
- Immune-related adverse events (irAEs) can affect any tissue; their incidence may reach up to 96% of patients;
- Nobel committee: improve understanding of irAEs
- Therapeutic paradigm shift: autoimmune T cells can be harnessed for a graft-versus-tumour (GVT) reaction by an off-label low-dose combined checkpoint blockade, complemented with interleukin 2 (IL-2) and hyperthermia;
- Overall response rate 48% with irAEs of WHO grade III and IV in 7% and 2% of 111 stage IV cancer patients

For survival T cells require regular stimulation from self-peptides



- Self-antigens activate T cells by "tonic" TCR signals
- **Physiologic autoimmunity regulated by checkpoint inhibitors**
- Following short activation T cells express CTLA-4 that terminates activation

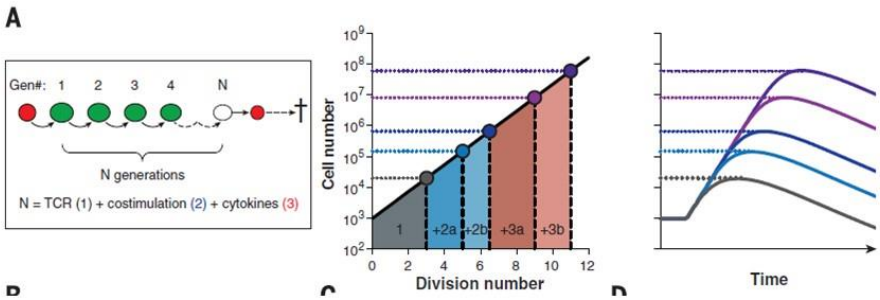
Immune checkpoint blockade turns physiologic autoimmunity into a pan-lymphocytic activation



- CTLA-4 is blocked not only on tumor-specific but on all activated T cells
- This results in immune stimulation, tolerance breakdown and tumor eradication
- **Cancer regressions cannot be achieved without breaking the tolerance**

Rationale for low-dose ICI combination therapy: individual (sub-threshold) effects add up

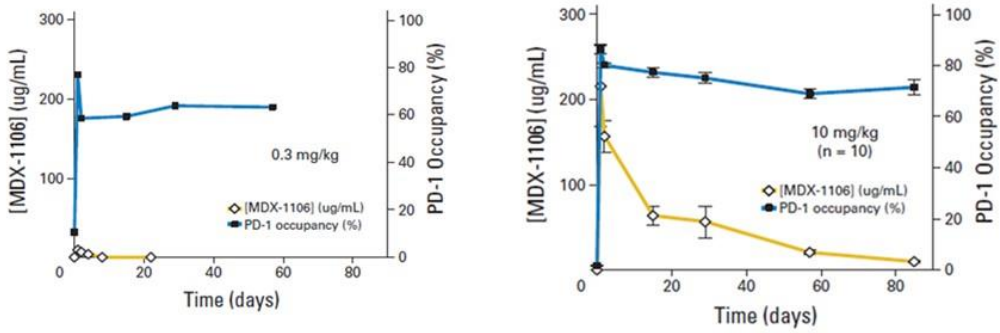
The quantitative paradigm of T cell activation: signals from the TCR, co-stimulatory/co-inhibitory receptors and cytokines are added together



Marchingo et al. Science. 2014 Nov 28;346:1123-7

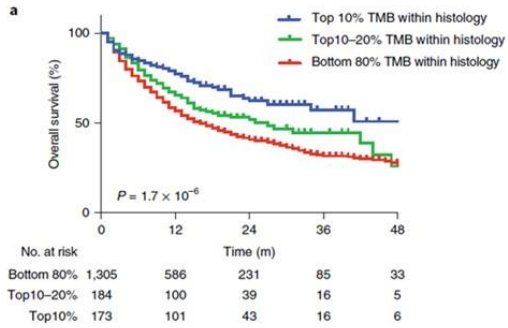
Off-label, low-dose ICI therapy administers the lowest doses (0.3 mg/kg ipilimumab and 0.5 mg/kg nivolumab)

PD-1 occupancy was comparable at **0.3 mg/kg and 10.0 mg/kg**



No patient had an antitumor response but had Gr 2/3 irAEs

Checkpoint inhibitors were more likely to halt tumor growth with higher number of mutations

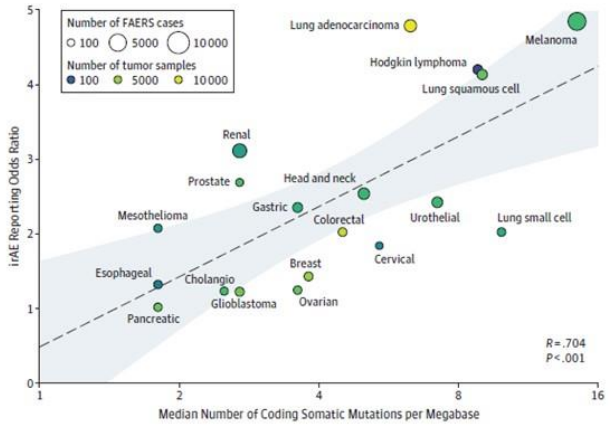


- ❑ Nature: neoantigens generate an immune reaction
- ❑ We suggest: this is a transplantation reaction against new antigens
- ❑ Without ICI blockade too weak to provoke T cell attack
- ❑ **With ICI blockade T cells attack semi-allogeneic tumors resulting in better overall survival**

Samstein, R.M., et al. Nat. Genet. 51:202–6, 2019.

Significant positive correlation between irAEs during anti–PD-1 therapy and TMB across multiple cancer types

Figure. Association of Tumor Mutational Burden With Immune-Related Adverse Events During Anti–PD-1 Therapy Across Multiple Cancers



Bomze, D., Hasan Ali, O., Bate, A., Flatz, L. 2019. Association Between Immune-Related Adverse Events During Anti–PD-1 Therapy and Tumor Mutational Burden. JAMA Oncology.

Insisting that ipilimumab is tumor specific is ignoring the obvious

Managing toxicities associated with immune checkpoint inhibitors Puzanov et al, Journal for Immunotherapy of Cancer, 2017

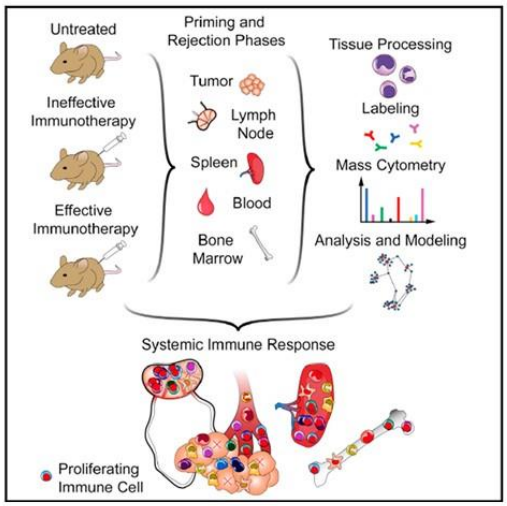
- ❑ irAEs affect any tissue, incidence up to 96%
- ❑ Overall incidence <75% with ipilimumab monotherapy; ≤30% anti-PD-1/PD-L1 agents
- ❑ IrAEs of ≥ grade 3 up to 43% with ipilimumab and ≤20% with PD-1/PD-L1 agents
- ❑ Combination of ipilimumab with nivolumab: 55% of grade 3/4 irAEs; discontinuation rate 30%
- ❑ irAEs with ipilimumab and pembrolizumab is dose-dependent
- ❑ Death due to irAEs occurred in up to 2% of patients

Autoimmunity is the Achilles' heel of cancer immunotherapy

- ❑ **Incidence of irAEs is underestimated**
  - ✓ most cancer trials follow patients for only a brief time
  - ✓ patients who died from their cancer are not included
- ❑ Incidence of irAEs will rise as these therapies become more widely used
- ❑ The risks of the ICIs is „a massively understudied area”

Systemic immunity is critical to tumor rejection following immunotherapy

Spitzer et al. Cell; 2017 Jan 26;168:487-502 e15



- High-throughput and high-dimensional single-cell technologies (mass cytometry, assessing all immune cells simultaneously)
- Supports therapeutic paradigm shift to exploit systemic autoimmunity for the treatment of advanced cancer

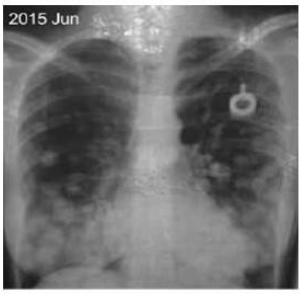
ICI antibodies generate Graft-Versus-Tumor (GVT) effect without allogeneic hematopoietic stem cell transplantation

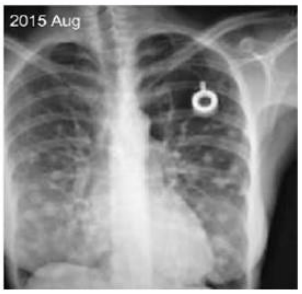
The same GVT effect could be achieved by ipilimumab as by donor lymphocyte infusion but without severe GVHD

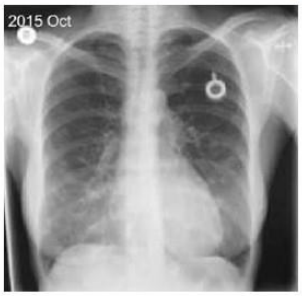
- While a low-dose adjuvant ipilimumab (0.3 mg/kg) could induce auto-GVHD… (Slavin et al, Pharmacol Res, 2013)
- …a high-dose (10 mg/kg) adjuvant ipilimumab gained FDA approval (33.3 times higher dose than that of suggested by Slavin) (Eggermont et al, N Engl J Med, 2016) with 41.6% of a grade 3 or 4 irAEs in the ipilimumab group, but only in 2.7% in the placebo group; 5 patients (1.1%) died due to irAEs of ipilimumab
- Since our low-dose ICI protocol consists only of approved drugs and treatments it can be confirmed or refuted in controlled clinical trials

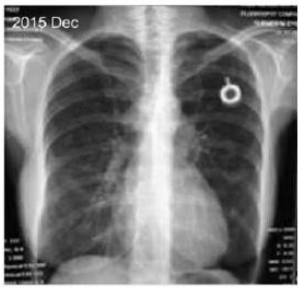
Complete remission of lung metastases in TNBC

Transient WHO I-II diarrhea and skin rash, patient alive for 27 months









ipilimumab (0.3 mg/kg) **nivolumab** (0.5 mg/kg)
interleukin-2 (54 Mio/m2 as decrescendo regimen)
loco regional- and whole body **hyperthermia**

Kleef et al Integrative Cancer Therapies, 2018
DOI: 10.1177/1534735418794867

Since the treatment of the first TNBC patient, 111 stage IV cancer patients were treated with a variety of cancer types

- ❑ Efficacy: **OR was 48%** with an ORR of 33%; the median follow-up 22 months
- ❑ Excellent safety: irAEs of WHO grade I in 21% of patients, grade II in 14%, **grade III in 7%, while grade IV in only 2% of patients**.
- ❑ With registered doses of ipilimumab (3 mg/kg) and nivolumab (3 mg/kg): irAEs in 96%, grade 3 or 4 irAEs in 55%, including events in the central nervous system in 7%; one patient died from immune-related myocarditis

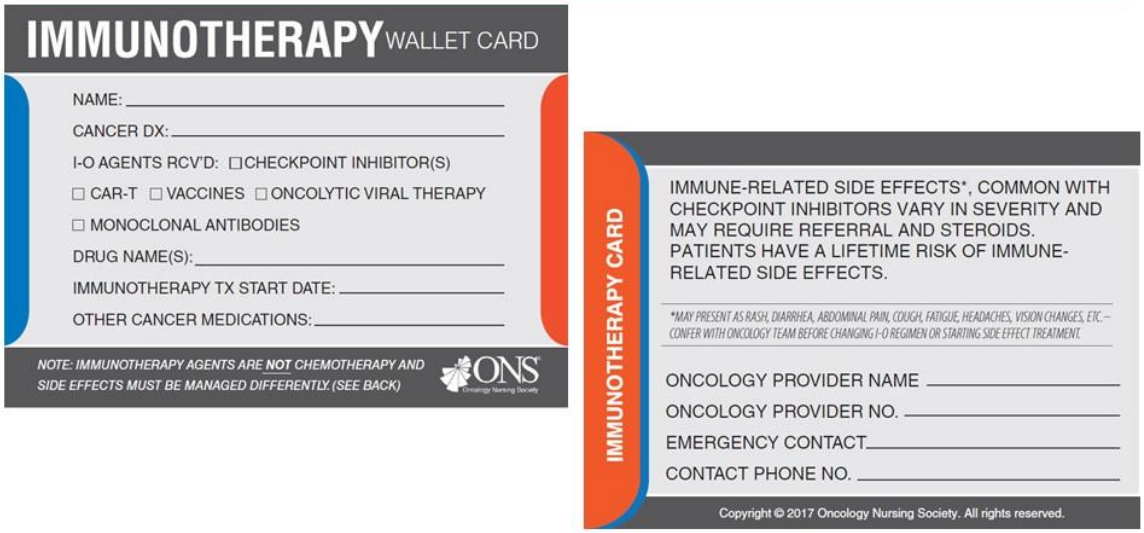
A retrospective analysis of single cases presented at the 8th-annual Oncology Association of Naturopathic Physicians in San Diego, CA, 2019.

Management of irAEs in Patients Treated With ICI Therapy: ASCO Clinical Practice Guideline.

J Clin Oncol. 2018

- ❑ Higher doses produce higher rates of irAEs
- ❑ Combination anti–CTLA-4 and anti–PD-1 significantly increased the risk of grade 3 and 4 irAEs
- ❑ The potential for life-disabling irAEs that are severe and/or irreversible exists
- ❑ **Dose reductions of immune checkpoint therapy should be avoided**

Patients often deny their symptoms when they fear their treatment will be stopped due to irAEs



IMMUNOTHERAPY WALLET CARD

NAME: _____

CANCER DX: _____

I-O AGENTS RCV'D: ☐CHECKPOINT INHIBITOR(S)

☐ CAR-T ☐ VACCINES ☐ ONCOLYTIC VIRAL THERAPY

☐ MONOCLONAL ANTIBODIES

DRUG NAME(S): _____

IMMUNOTHERAPY TX START DATE: _____

OTHER CANCER MEDICATIONS: _____

NOTE: IMMUNOTHERAPY AGENTS ARE NOT CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY. (SEE BACK)

ONS Oncology Nursing Society

IMMUNOTHERAPY CARD

IMMUNE-RELATED SIDE EFFECTS*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

**MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.– CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.*

ONCOLOGY PROVIDER NAME _____

ONCOLOGY PROVIDER NO. _____

EMERGENCY CONTACT _____

CONTACT PHONE NO. _____

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy, Brahmer et al, J Clin Oncol, 2018

University of Texas M.D. Anderson Cancer Centre confirmed the rationale for our low-dose immune checkpoint blockade protocol

- Despite dose-dependent increase in irAEs, no improvement in PFS, OS, or DCR with escalating doses of ICIs.
- Lower doses may reduce toxicity and cost without compromising disease control or survival.

Financial toxicity of newer oncology drugs is an issue for patients and health systems

Less than 5% of the population has coverage for PD-1 in Peru and less than 10% in Chile

TABLE 3. Dose and Cost Estimations for Nivolumab

Nivolumab	0.1 mg/kg Once Every 2 Weeks	0.3 mg/kg Once Every 2 Weeks	1 mg/kg Once Every 2 Weeks	3 mg/kg Once Every 2 Weeks	240 mg Once Every 2 Weeks
Mg per cycle	8	24	80	240	240
Cost per cycle (USD)	205	615	2,051	6,153	6,153
Cost per year (USD)	4,922	14,766	49,221	147,663	147,663
Relative cost versus std (%)	3	10	33	100	100
Patients treated versus std (No.)	30	10	3	1	1

NOTE. Dose estimated for an 80-kg patient. Calculations consider a cost of US $25.63 per mg, per Centers for Medicare and Medicaid Services Medicaid information.[21] These calculations do not reflect total treatment cost because they only consider medication expenditures.
Abbreviations: std, standard dosage; USD, US dollars.

Renner, A., Burotto, M., Rojas, C. 2019. Immune Checkpoint Inhibitor Dosing: Can We Go Lower Without Compromising Clinical Efficacy? Journal of Global Oncology, 1.(ASCO)

Financial barrier should be reduced to benefit more patients

- ❑ Both pembrolizumab and nivolumab have significant efficacy at much lower doses than those approved
- ❑ This should be tested in RCT
- ❑ **It is unlikely the pharmaceutical industry will be interested in such a subject**
- ❑ Independent institutions, universities, or collaborative groups would have to take on this challenge

„As I go around the country, I talk about the tragedy of cancer to remind people that the tragedy is not our inability to prevent the inevitable or to do the impossible; tragedy is when a person, a group or a society fails to achieve the possible."


Cancer

Remark | Free Access

Cancer, minorities & the medically underserved*

The role of the National Cancer Institute

Richard D. Klausner M.D.

First published: 09 November 2000

Thank you for your attention

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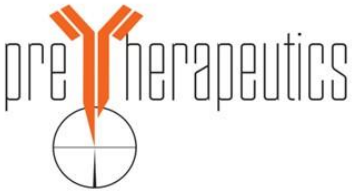
Dr. Tibor BAKACS, Chief Scientific Officer tiborbakacs@gmail.com



Hyperthermia as part of multimodal immunotherapy for patients with GBM

Stefaan Van Gool[1], Jennifer Makalowski[1], Marija Marko[1], Wilfried Stuecker[1]

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Presented at the 37th ICHS, Thessaloniki

Cite this article as:

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www.oncotherm.com/sites/oncotherm/files/2019-10/Hperthermia_as_part_of_multimodal.pdf

Introduction.
The prognosis for patients with glioblastoma multiforme (GBM) remains poor in spite of modern neurosurgery, radiotherapy and addition of chemotherapy. Results from the use of checkpoint blockers are disappointing. There is need for active immunization strategies in order to create an anti-tumor immune effector function and an immune memory against GBM for the installation of long-term protection.

Objectives
We integrated 5-day treatments with injections of Newcastle Disease Virus (NDV) and moderate modulated electrohyperthermia (mEHT, 50 min, 40-55 Watt) into the maintenance chemotherapy with 5 days temozolomide (TMZ), after which we continued with full vaccination cycles including NDV injections, mEHT sessions, autologous DC vaccinations with IO-VAC® and immunomodulatory strategies. The objective of this study is to report on the results obtained from patients receiving such complex individualized combination treatment.

Material/Methods
We found in our database (01/05/2019) 71 adults with primary GBM treated with multimodal immunotherapy as part of the first line treatment. For 34 adults, NDV and hyperthermia was administered during TMZ maintenance chemotherapy.

Results
There were 10 females and 24 males with median age of 58 years (range 20-67). Median Karnofsky performance scale was 75 (range 60-100). Six patients are still under treatment. In median, 2 (range 0-13) DC vaccines, 25 (range 0-117) hyperthermia treatments and 28 (range 7-115) NDV injections were administered. Five from 28 patients who finished immunotherapy did not reach DC vaccination due to progressive disease. Median PFS was 10.46 months. Median OS was 23.44 months with 2-year OS of 48% (CI95%: +18, -20). There were no major treatment-related toxicities.

Conclusion
Multimodal immunotherapy including moderate modulated electrohyperthermia is feasible for patients with first diagnosis of primary GBM. The treatment can be integrated in the standard therapy and continues thereafter. Median PFS and OS, and more importantly the % long-term OS seem to be improved. The data can form a basis for a prospective controlled clinical trial.

Hyperthermia as part of multimodal immunotherapy for patients with GBM

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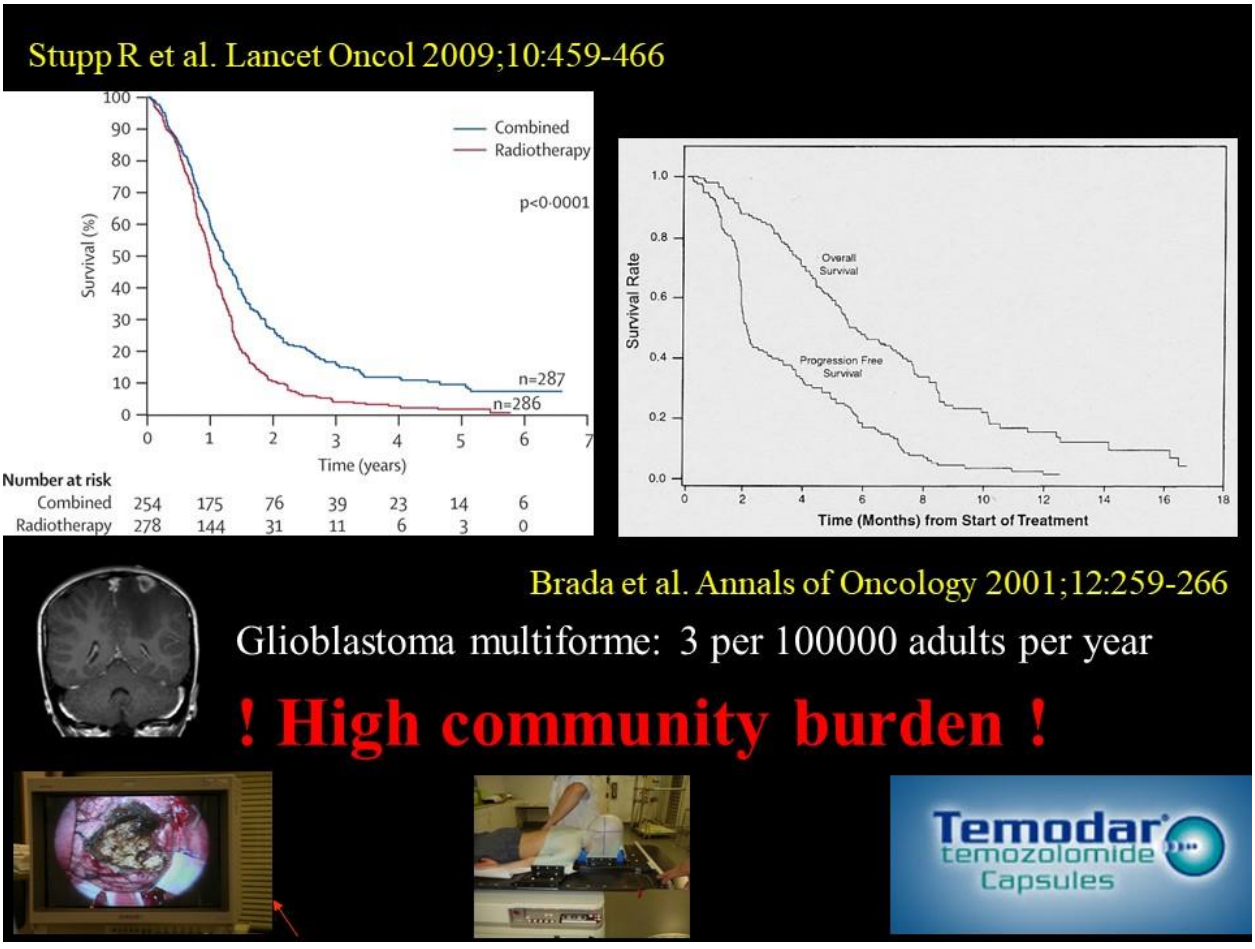
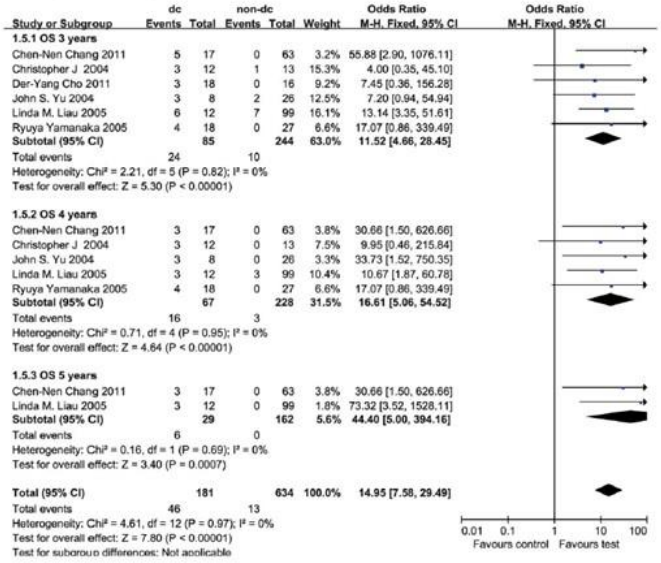


OPEN ACCESS Freely available online

PLOS ONE

Clinical Efficacy of Tumor Antigen-Pulsed DC Treatment for High-Grade Glioma Patients: Evidence from a Meta-Analysis

Jun-Xia Cao[1,2]*, Xiao-Yan Zhang[1], Jin-Long Liu[1], Duo Li[1], Jun-Li Li[1], Yi-Shan Liu[1], Min Wang[1], Bei-Lei Xu[1], Hai-Bo Wang[1], Zheng-Xu Wang[1]*



IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Dendritic Cell-Based Vaccine for the Treatment of Malignant Glioma: A Systematic Review

Xuan Wang, Hong-Yang Zhao, Fang-Cheng Zhang, Yun Sun, Zhi-Yong Xiong & Xiao-Bing Jiang

To cite this article: Xuan Wang, Hong-Yang Zhao, Fang-Cheng Zhang, Yun Sun, Zhi-Yong Xiong & Xiao-Bing Jiang (2014) Dendritic Cell-Based Vaccine for the Treatment of Malignant Glioma: A Systematic Review, Cancer Investigation, 32:9, 451-457, DOI: 10.3109/07357907.2014.958234

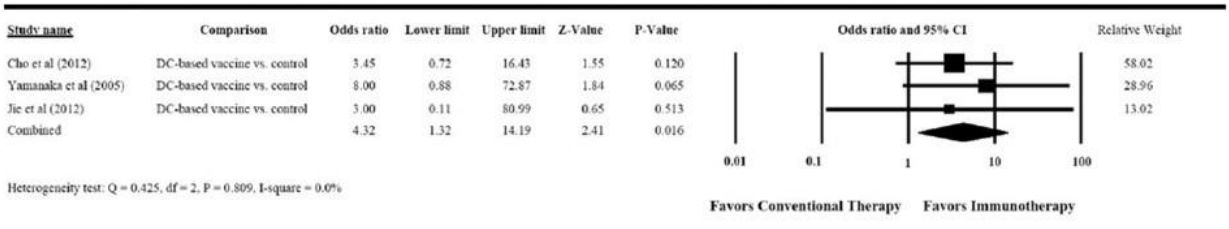


Figure 2. Meta-analysis of 2-year survival.

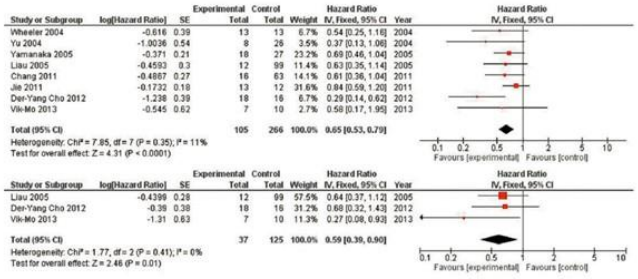


Figure 1. OS (a) and PFS (b) hazard ratios for trials using DC vaccination versus standard of care.

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

JOURNAL OF IMMUNOASSAY AND IMMUNOCHEMISTRY
2019, VOL. 40, NO. 1, 70–80
https://doi.org/10.1080/15321819.2018.1551804

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Assessment of efficacy of dendritic cell therapy and viral therapy in high grade glioma clinical trials. A meta-analytic review

Bogdan Ionel Vatu[a], Stefan-Alexandru Artene[a], Adeline-Georgiana Staicu[a], Adina Turcu-Stiolica[b], Catalin Folcuti[a], Alexandra Dragoi[a], Catalina Cioc[a], Stefania-Carina Baloi[a], Ligia Gabriela Tataranu[c], Cristian Silosi[d], and Anica Dricu[a]

[a]Department of Biochemistry, University of Medicine and Pharmacy of Craiova, Craiova, Romania; [b]Department of Biostatistics, University of Medicine and Pharmacy of Craiova, Craiova, Romania; [c]Department of Neurosurgery, Carol Davila, University of Medicine and Pharmacy, Bucharest, Romania; [d]Department of Surgery, University of Medicine and Pharmacy of Craiova, Craiova, Romania

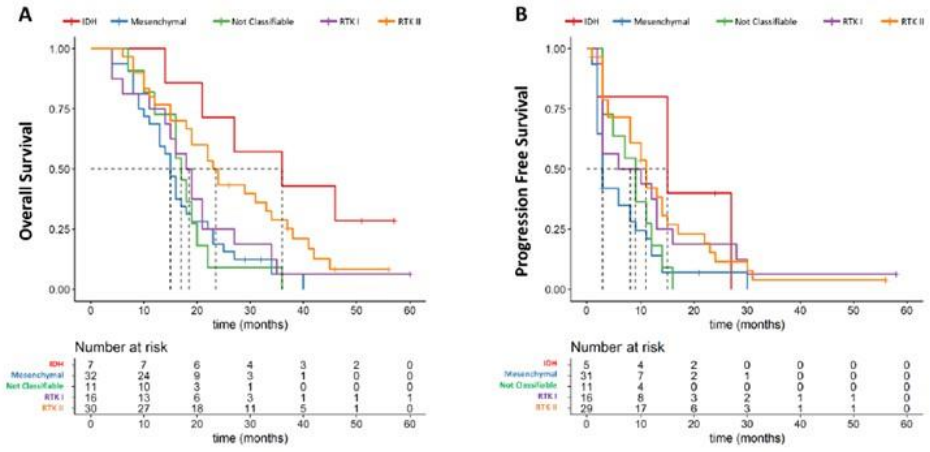

Figure 2: *Kaplan-Meier graph showing Overall Survival (**A**) and Progression-free Survival (**B**) for the 5 DNA methylation based subgroups of GBM patients. The vertical lines display the median survival time for both groups: Median PFS and OS were 15.0 and 36.0 months in the IDH group respectively, 3.0 and 15.0 in the mesenchymal, 8.0 and 18.5 in the RTK I, 11.0 and 23.5 in RTK II and 9.0 and 17.0 in Not Classifiable tumors.*

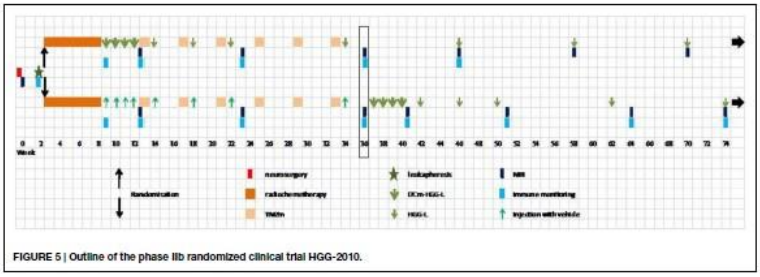

FIGURE 5 | Outline of the phase IIb randomized clinical trial HGG-2010.

		Multivariate analysis		
methylation subclassification				0.05
	IDH	#	#	#
	mesenchymal	3.61	1.25 - 10.46	0.02
	not classifiable	4.10	1.22 - 13.73	0.02
	RTK I	2.70	0.90 - 8.15	0.08
	RTK II	1.92	0.68 - 5.44	0.22
Age at resection		1	0.97 - 1.03	0.97
Early vs late vaccination				0.58
	Early	#	#	#
	Late	0.87	0.53 - 1.43	0.58
EOR				0.12
	Partial	#	#	#
	Subtotal	0.64	0.29 - 1.42	0.27
	Total	0.47	0.22 - 1.01	0.05
MGMT promotor methylation				< .001
	Methylated	#	#	#
	Unmethylated	2.95	1.77 - 4.93	< .001
	Not determinable	1.93	0.73 - 5.09	0.19

Table 2: *Multivariate analysis of Overall Survival of different DNA methylation tumor subgroups, adjusted for age at resection, EOR, early versus late vaccination and MGMT promotor methylation in a Cox proportional hazard model. CI = Confidence Interval.*

ANTICANCER RESEARCH *39*: 2043-2051 (2019)
doi:10.21873/anticanres.13315

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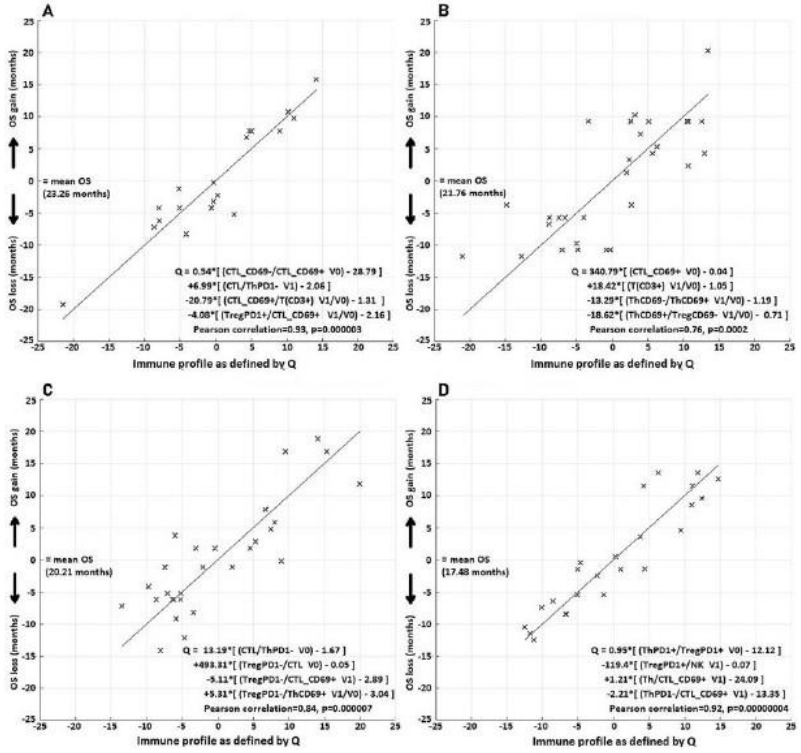


Figure 2. *Canonical correlation analysis of immune profiles versus overall survival (OS). The immune profile is composed of the different FACS-derived quantities (features). Diagrams for four subgroups are shown. A: Vaccination during temozolomide maintenance chemotherapy (TMZm), no residual tumor volume after resection; B: vaccination after TMZm, no residual tumor volume after resection; C: vaccination during TMZm, non-zero residual tumor volume after resection; D: vaccination after TMZm, non-zero residual tumor volume after resection. Each diagram depicts the strong correlation between Q (x-axis), where Q is the sum of quantities of the form: coefficient × [feature − mean of feature in the specific subgroup], and OS (y-axis) expressed as the quantity OS being the individual OS in months minus the mean OS, i.e. mean OS for the specific subgroup.*

Table I. *Overall survival (OS) data of the total study population and subgroups residual tumor volume (RTV).*

Patient group	No. of patients	Median OS (months)	2-Year OS rate (%)	95%CI
Total group	101	19	33.66	24.66-42.88
Early vaccination, RTV=0	19	22	40.2	18.4-61.2
Late vaccination, RTV=0	29	23	44.8	26.5-61.5
Early vaccination, RTV>0	28	19	25	11-41.7
Late vaccination, RTV>0	25	16	28	12.4-46

Challenges

- What if the tumor tissue is not available
- The tumor tissue is a heterogeneous dynamic phenomenon with glioma cancer stem cells and with emerging and disappearing tumor cell clones
- Need for improved combination treatments in and outside immunotherapy adapted to the situation/need of the patient, conflict with statistical designs
- Increasing demand, increasing immuno-oncologic insights <-> conflict with financial and regulatory restrictions

- Oncolytic virus and modulated electrohyperthermia → ICD
- ICD→ actual panel of antigenic extracellular microvesicles
- Shift towards individualized treatment approaches
- From Research & Development towards controlled Implementation

Strategies forward

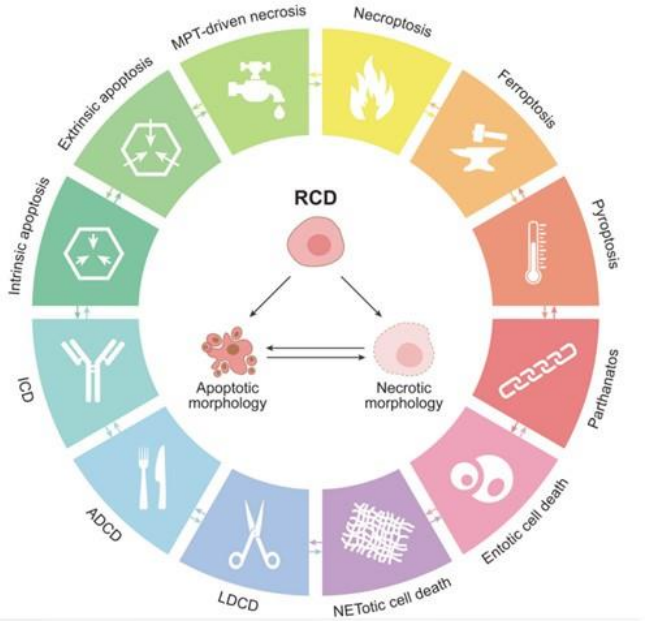
Cell Death & Differentiation
https://doi.org/10.1038/s41418-017-0012-4

Cell Death & Differentiation

REVIEW

Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi[1,2,3] · Ilio Vitale[4,5] et al.



Galluzzi et al. Consensus guidelines for the definition, detection and interpretation of immunogenic cell death, in preparation

frontiers in Immunology

REVIEW

Exploiting the Immunogenic Potential of Cancer Cells for Improved Dendritic Cell Vaccines

Lien Vandenberk[1*], Jochen Belmans[1], Matthias Van Woensel[2,3], Matteo Riva[1,4] and Stefaan W. Van Gool[1,4,5*]

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biomedicines

MDPI

Review

Breaking Therapy Resistance: An Update on Oncolytic Newcastle Disease Virus for Improvements of Cancer Therapy

Volker Schirrmacher *, Stefaan van Gool and Wilfried Stuecker

Immune-Oncological Center Cologne (IOZK), D-50674 Cologne, Germany
* Correspondence: V.Schirrmacher@web.de

Received: 30 July 2019; Accepted: 23 August 2019; Published: 30 August 2019

Abstract: Resistance to therapy is a major obstacle to cancer treatment. It may exist from the beginning, or it may develop during therapy. The review focusses on oncolytic Newcastle disease virus (NDV) as a biological agent with potential to break therapy resistance. This avian virus combines, upon inoculation into non-permissive hosts such as human, 12 described anti-neoplastic effects with 11 described immune stimulatory properties. Fifty years of clinical application of NDV give witness to the high safety profile of this biological agent. In 2015, an important milestone was achieved, namely the successful production of NDV according to Good Manufacturing Practice (GMP). Based on this, IOZK in Cologne, Germany, obtained a GMP certificate for the production of a dendritic cell vaccine loaded with tumor antigens from a lysate of patient-derived tumor cells together with immunological danger signals from NDV for intracutaneous application. This update includes single case reports and retrospective analyses from patients treated at IOZK. The review also presents future perspectives, including the concept of in situ vaccination and the combination of NDV or other oncolytic viruses with checkpoint inhibitors.

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Molecular Therapy
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Pre-existing Immunity to Oncolytic Virus Potentiates Its Immunotherapeutic Efficacy

Jacob M. Ricca,[1,2] Anton Oseledchyk,[4] Tyler Walther,[1,2] Cailian Liu,[1,2] Levi Mangarin,[1,2,3] Taha Merghoub,[1,2,3] Jedd D. Wolchok,[1,2,3,5] and Dmitriy Zamarin[1,2,3,5]

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Journal of Cancer 2018, Vol. 9 41

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2018; 9(1): 41-53. doi: 10.7150/jca.21520

Research Paper

Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts

Tamas Vancsik[1], Csaba Kovago[2], Eva Kiss[1], Edina Papp[3], Gertrud Forika[1], Zoltan Benyo[4], Nora Meggyeshazi[1]*, Tibor Krenacs[1]*✉

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2. Department of Pharmacology and Toxicology, Faculty of Veterinary Science, St. Istvan University, Budapest, Hungary;
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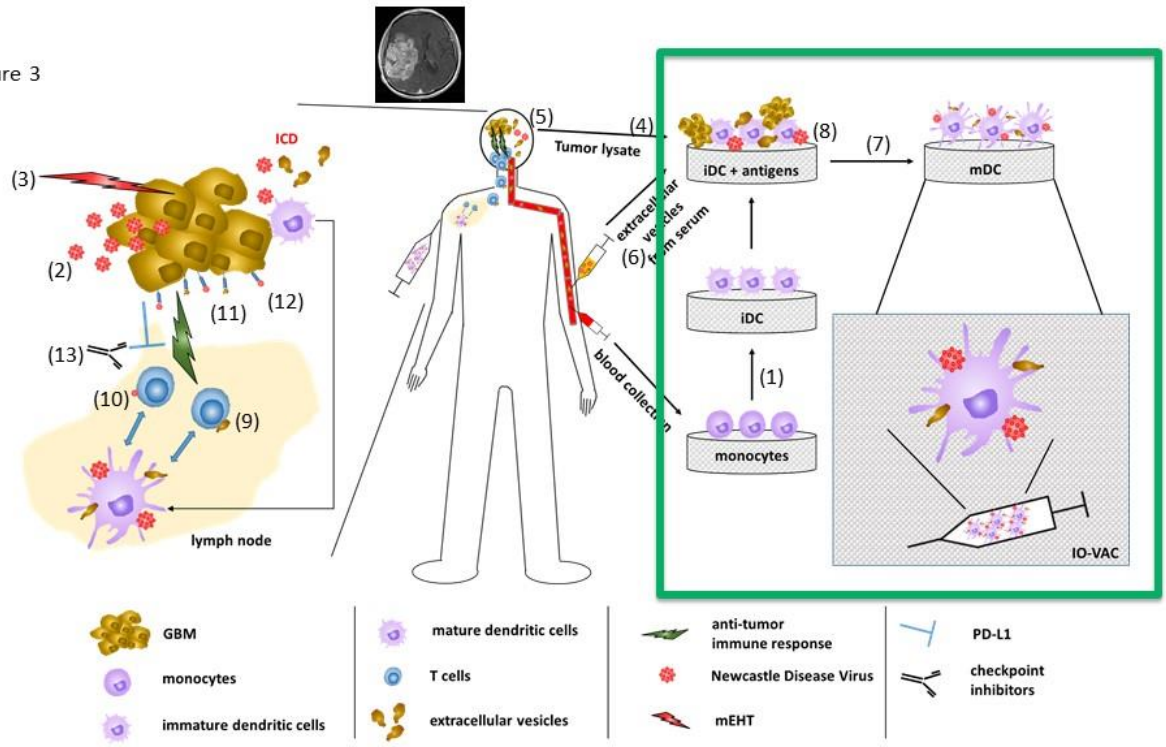
Dosierung

- Erwachsenen
  1. Bei der mittleren Sonde ist darauf zu achten, dass beim Beginn der Behandlung die Temperatur nur in kleinen Schritten gesteigert werden sollte. Die Leistung sollte mit Modulation in 5 W Schritten (höchstens 10 W) langsam erhöht werden in zeitabständen von ca. 10 Minuten[1]. Diese kontinuierliche Erhöhung sollte sich über den gesamten Behandlungszeitraum von 50 Minuten bei Erwachsenen erstrecken. Erste Tag 30 Minuten.
  2. Die gleiche Vorgehensweise gilt auch für die große Sonde, falls diese zum Einsatz kommen sollte. Bei der großen Sonde wird die Behandlungstemperatur grundsätzlich in 20 W Schritten erhöht. Auch hier sollte die Temperatur bzw. die Leistung der Sonde spätestens nach 10 Minuten erhöht werden. Behandlungszeitraum von 50 Minuten. Erste Tag 30 Minuten.
- Kindern

  Bei Kindern, die behandelt werden, dauert die Behandlung grundsätzlich nur 40 Minuten bei einer Leistung der Sonde. Erste Tag 20 bis 30 Minuten.

	Tag 1	Nach Tag 1
Kopf. Modulation.		
Kind	40 W 20-30 Min	40 (20 Min) --> 60 W bis 40 Min
Erwachsene	40 W 30 Min	40 (20 Min) --> 60 W bis 50 Min
Körper. Modulation.		
Kind	40 W 20-30 Min	40 (20 Min) --> 60 W bis 40 Min
Mittlere Sonde	40-60 W 30 Min	40-60 --> 80 --> 90 (Prostata) --> 100 (--> 120) W 50 Min
Große Sonde	60-100 W 30 Min	60-100 --> 140 --> 150 W 50 Min

Figure 3



E-Book, Cambridge Scholars Publishing, in press

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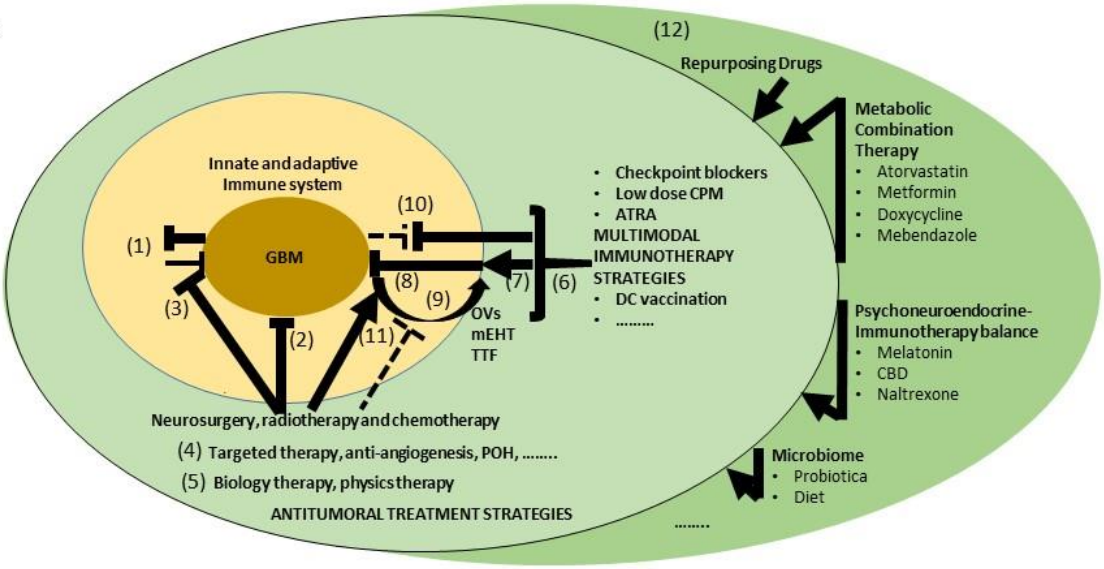
Figure 6



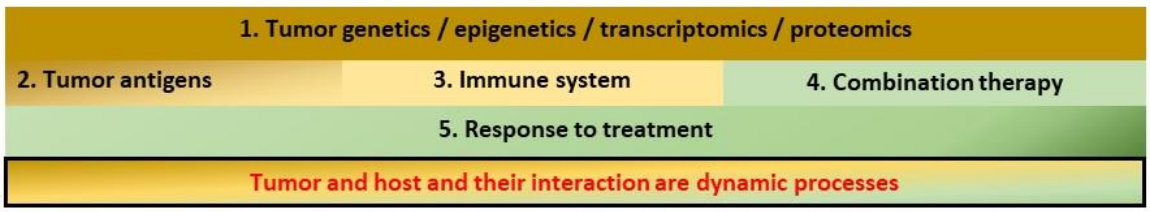


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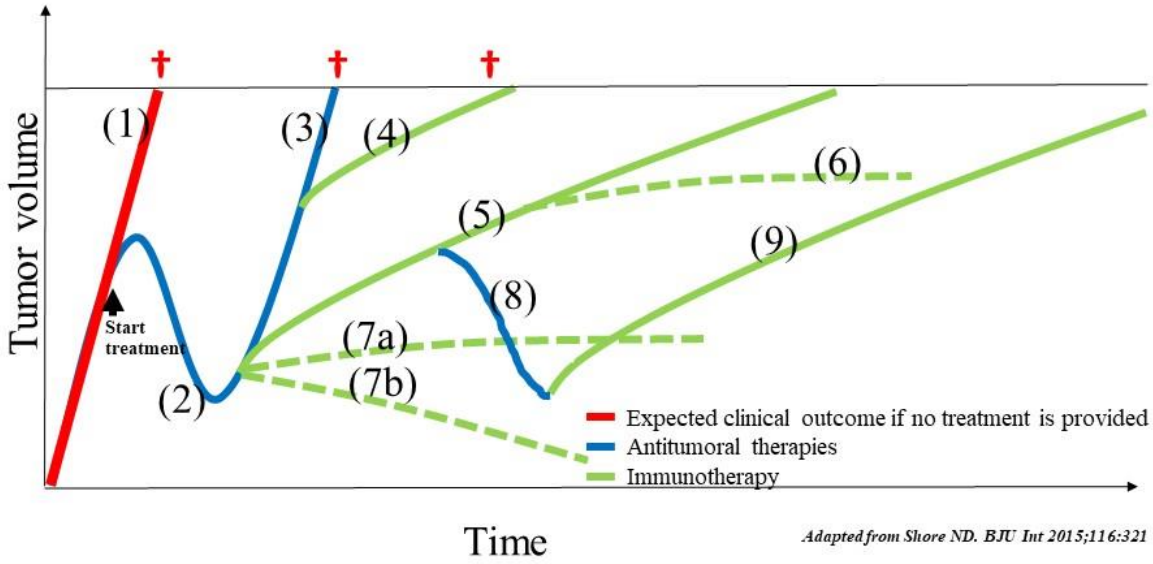
Figure 2

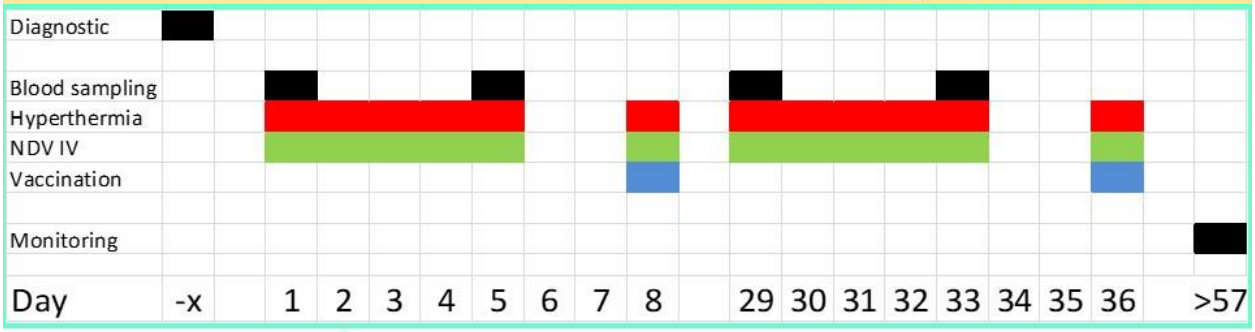


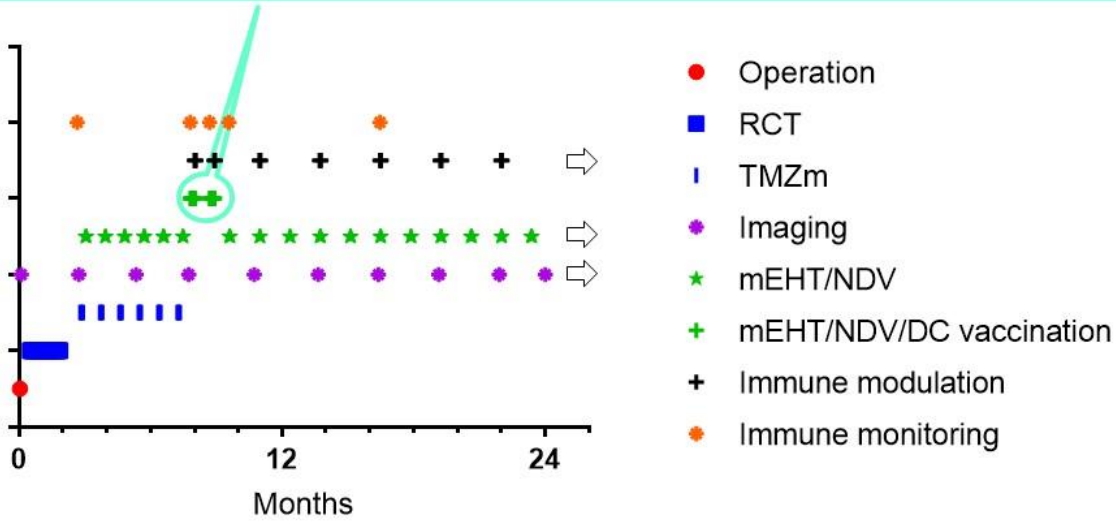
Adapted from Shore ND. BJU Int 2015;116:321

Ideal scenario = early start with multimodal immunotherapy

Antitumor strategy
Surgery (-> R(C)T + CT)
Multimodal immunotherapy

E-Book, Cambridge Scholars Publishing, in press

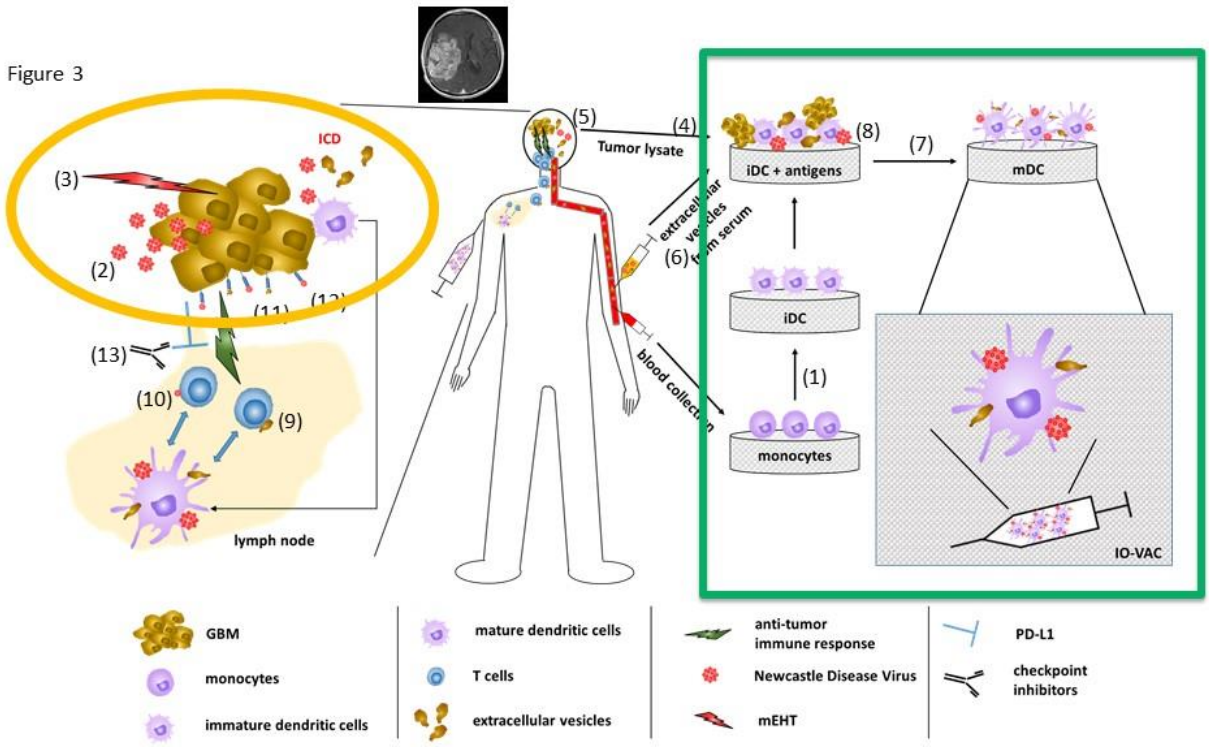




Van Gool SW, et al. AOCR 2018

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

Figure 3



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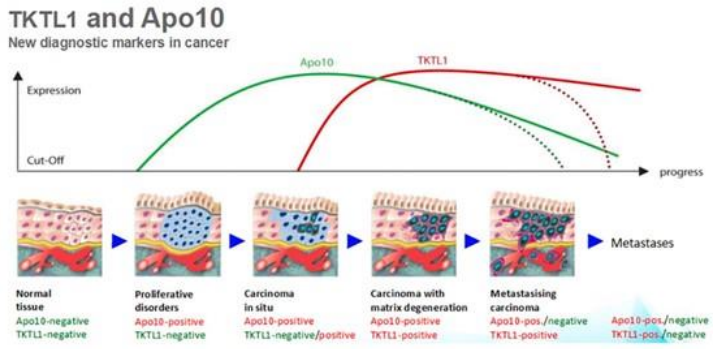

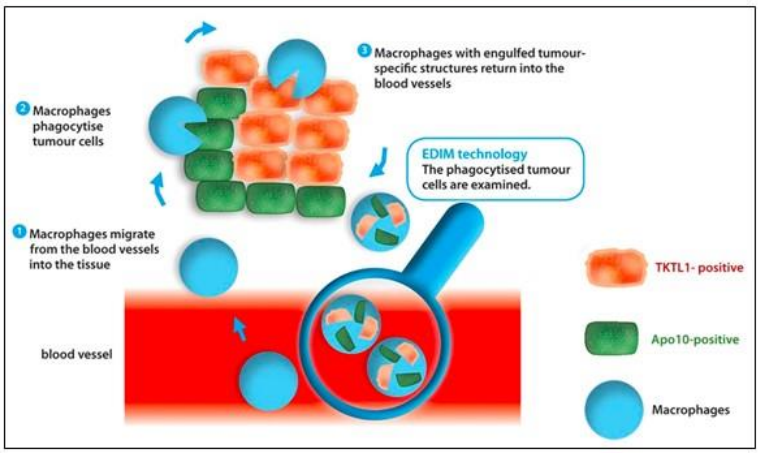

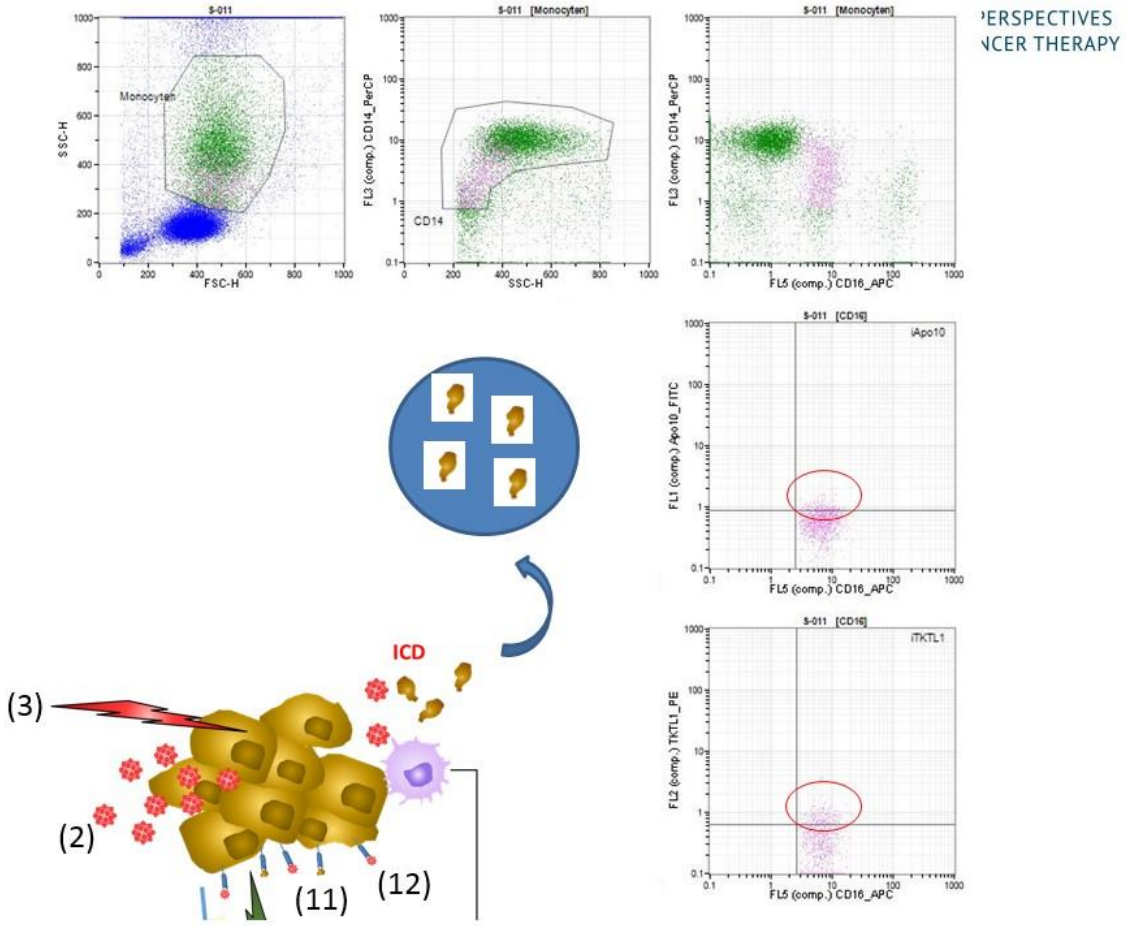
S-011
Monocyten
SSC-H
FSC-H
S-011 [Monocyten]
FL3 (comp.) CD14_PerCP
CD14
SSC-H
S-011 [Monocyten]
FL3 (comp.) CD14_PerCP
FL5 (comp.) CD16_APC
S-011 [CD16]
Apo10
FL1 (comp.) Apo10_FITC
FL5 (comp.) CD16_APC
S-011 [CD16]
TKTL1
FL2 (comp.) TKTL1_PE
FL5 (comp.) CD16_APC
ICD
(3)
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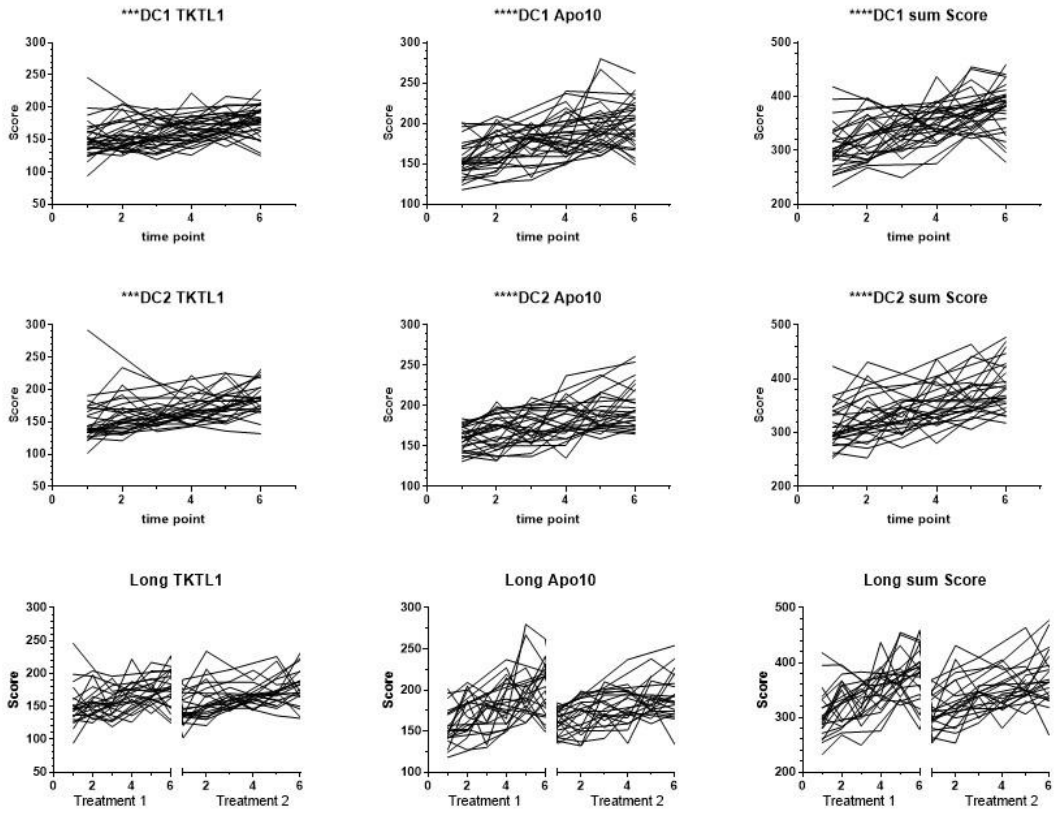
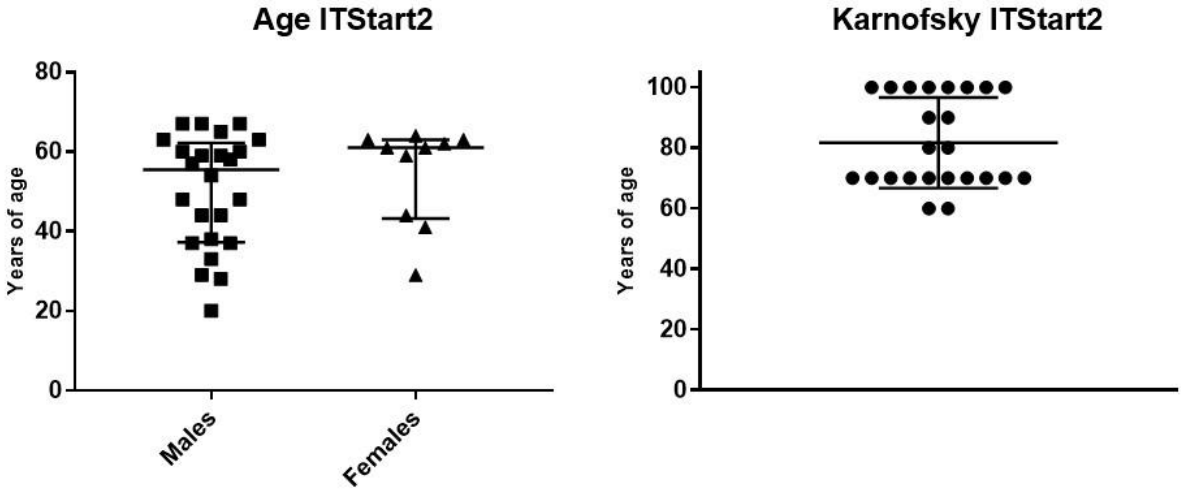

***DC1 TKTL1
****DC1 Apo10
****DC1 sum Score
***DC2 TKTL1
****DC2 Apo10
****DC2 sum Score
Long TKTL1
Long Apo10
Long sum Score
Score
time point
Treatment 1
Treatment 2



*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

01/05/2019

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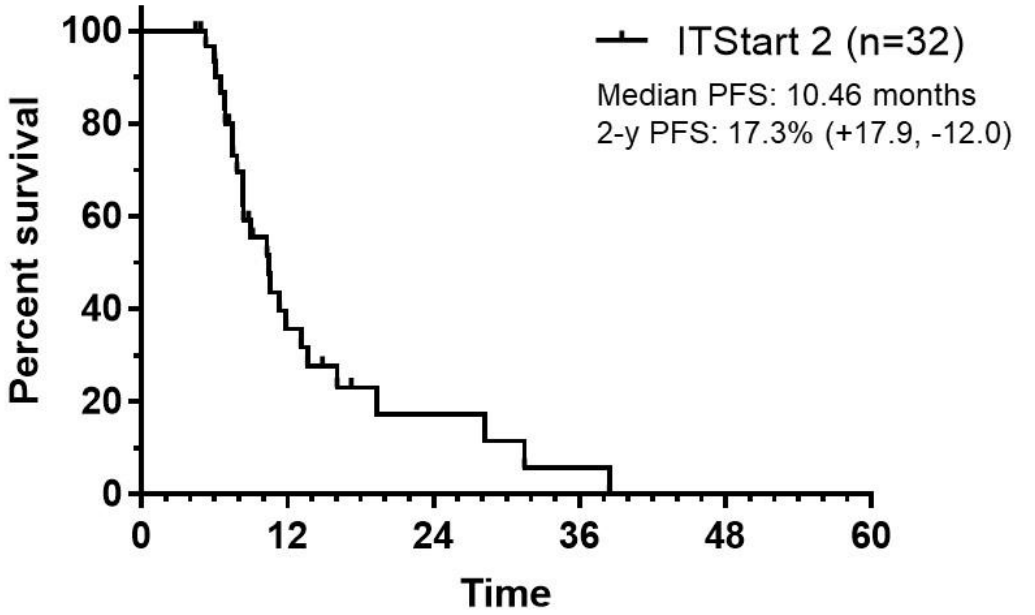
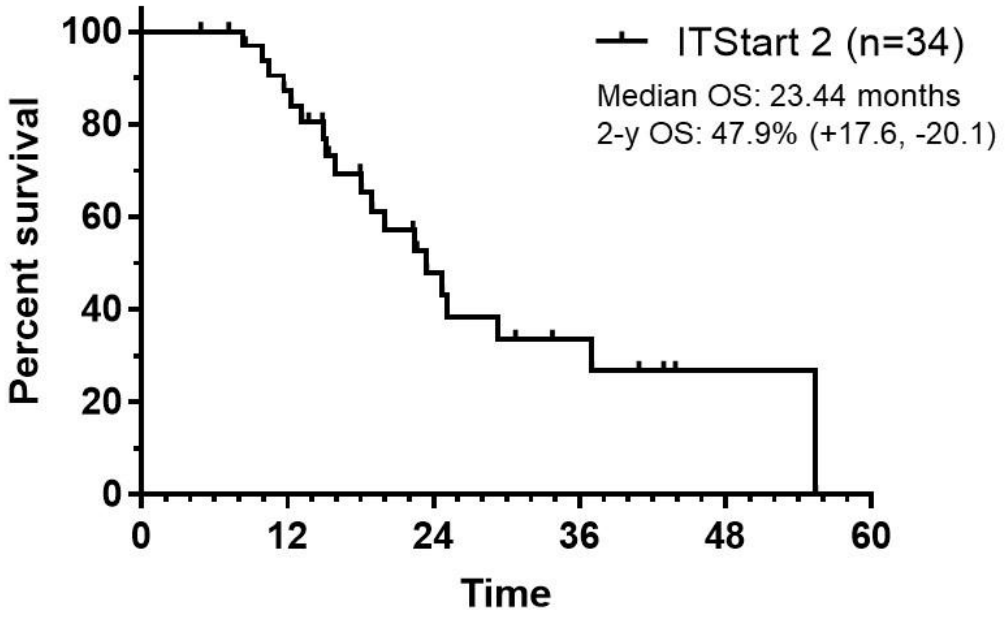


*Retrospective summary of patients treated as „**Individueller Heilversuch**“*



*Retrospective summary of patients treated as „**Individueller Heilversuch**"*

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Perspectives

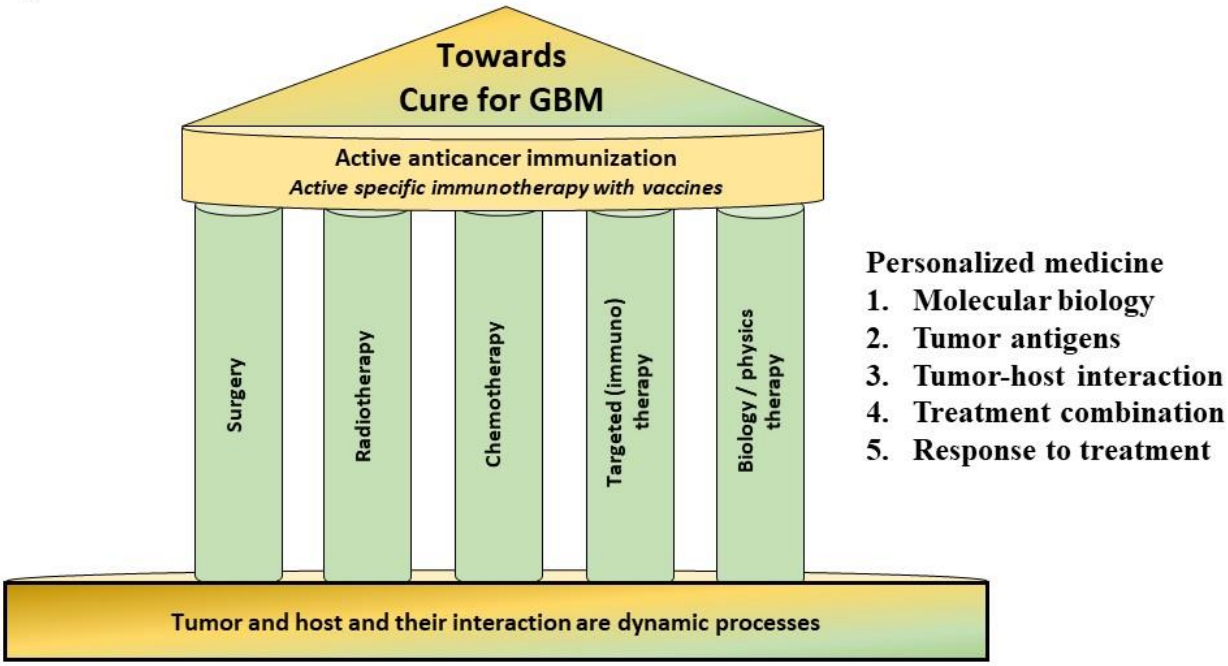
- IO-VAC®, IO-VAC-P®, IO-VAC-P+®: collaboration with CeGaT, Tübingen
- Defined Neo-epitopes → improved immune monitoring

- Improved immune phenotyping prior to and during multimodal immunotherapy
- Day by day ICD monitoring
- **Quid: research project within the Hyperthermia Community ??**

- Further integration of ICD therapy (NDV injections + modulated electrohyperthermia) within first line treatment combinations, also for other cancer diseases

- **Hope**: find answers how to solve clinical trial challenges (organisation, statistics, regulation, finances)

Figure 1



E-Book, Cambridge Scholars Publishing, in press

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Multimodal immunotherapy for patients with ovarian cancer

Stefaan Van Gool[1], Jennifer Makalowski[1], Marija Marko[1], Wilfried Stuecker[1]

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Presented at the 37th ICHS, Thessaloniki

Cite this article as:

Van Gool S. et al. (2019): Multimodal immunotherapy for patients with ovarian cancer, Oncothermia Journal 27: 138- 152
www.oncotherm.com/sites/oncotherm/files/2019-10/Multimodal_immunotherapy.pdf

Introduction
Ovarian cancer remains a serious disease with bad prognosis, mainly due to spreading disease before diagnosis. Surgery, chemotherapy, and anti-angiogenesis are essential for first line treatment. At time of relapse or metastasis, only palliative treatments can be performed. Active specific immunotherapy, however, give some glimpse of hope.

Objectives
The objective of this study is to report on our experiences obtained from ovarian cancer patients receiving multimodal immunotherapy as individualized treatment approach.

Material/Methods
Since the approval in May 2015 for GMP production of autologous Dendritic cell vaccines loaded with autologous tumor antigens (IO-VAC®), patients with ovarian cancer were treated with multimodal immunotherapy, consisting of injections with Newcastle Disease Virus (NDV), modulated electrohyperthermia (mEHT), IO-VAC® and immunomodulatory strategies like ATRA, low dose cyclophosphamide or checkpoint blockers.

Results
We found in our database (01/05/2019) 9 females with ovarian cancer (5 serous, 2 mixed, 2 not documented). Median age at diagnosis was 39y (range 29-64y). Two patients included immunotherapy at time of first event, while the others presented at later events (1, 2 and 4 patients resp. at event 2, 3, 4). All except 2 patients presented with FIGOIIIB or higher. In median 2 (range 0-4) vaccination cycles with IO-VAC® were administered, 17 (range 7-43) sessions of NDV injections and mEHT treatments, and 1 (range 0-5) total body hyperthermia sessions. One patient received high dose ATRA to block myeloid-derived suppressor cells. At time of analysis, 5 patients were still alive and OS data were calculated from first diagnosis and from start IO-VAC®: Patient 1 (FIGO IV, Event 1): +44m, +40m; patient 2 (FIGO IIIC, Event 4): +133m, +20m; Patient 3 (FIGO IIIB, Event 3): +58m, +18m; Patient 4 (FIGO IIIC, Event 2): +29m, +7m; Patient 5 (FIGO IV, Event 4): +49m, +3m. Other 4 patients died: Patient 6 (FIGO IA, Event4): 37m, 4m; Patient 7 (FIGO IV, Event 1): 12m, 7m; Patient 8 (FIGO IIIC, Event 4): 69m, 2m; Patient 9 (FIGO IIB, Event 3): 75m; 11m. All treatments were performed in an ambulant setting. Treatment was feasible and safe. There were no toxicities.

Conclusion
Multimodal immunotherapy can contribute to improved OS. Further studies on larger groups of patients with longer follow up are needed to demonstrate the efficacy of multimodal immunotherapy in ovarian cancer.

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Multimodal immunotherapy for patients with ovarian cancer

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Ovarian cancer, the silent women killer

- World-wide: 200,000 women affected; 125,000 death of disease
- 1/78 women get ovarian cancer in their life-time
- Majority of women diagnosed at advanced disease stages III and IV

- Type I: 30%: genetically stable and slow-growing disease
  - Low-grade serous
  - Endometrioid
  - Clear cell
  - Mucinous
- Type II: 70%: genetically unstable and aggressive
  - High-grade serous

- Surgery and Platinum- + Taxane-based chemotherapy

1

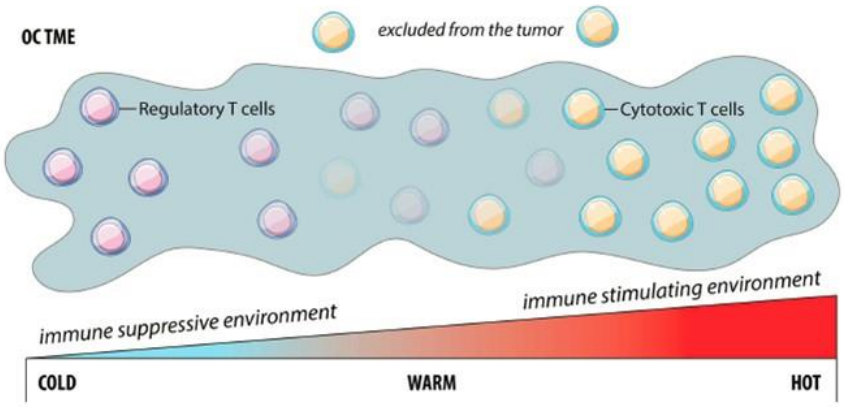

FIGURE 2 | The cold, warm or hot tumor microenvironment is a continuum. Cold tumors are characterized by the lack of cytotoxic T cells and are typically associated with an immune suppressive environment. Conversely, hot tumors are well infiltrated by cytotoxic T cells and are associated with an immune stimulating environment and better prognosis than the prior. However, the characterization of tumors is not dichotomous, but rather exists as a sliding scale of cytotoxic T cell infiltration with "warm" tumors representing a situation where although T cells exist, they are excluded and therefore ineffective at producing an efficient anti-tumor response.

Nersesian S et al. Front Immunol 2019;10:1782

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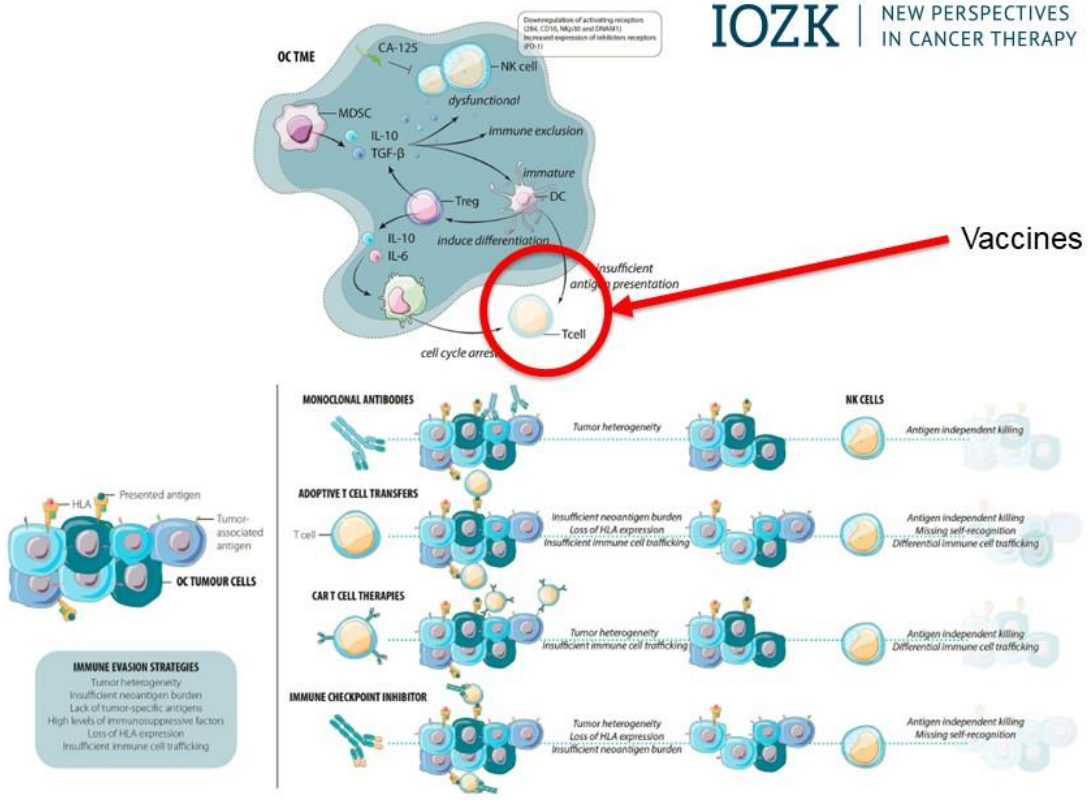

FIGURE 1 | Current immunotherapies frequently result in the persistence of a resistant cell population. This immune evasion of OC tumor cells can be facilitated by tumor heterogeneity, insufficient neoantigen burden, lack of tumor-specific antigens, high levels of immunosuppressive factors, loss of HLA, and/or insufficient immune cell trafficking. NK cells exhibit multiple functions that combat immune escape and tumor relapse: they kill targets and elicit inflammation through both antigen-specific and antigen-independent pathways and detect loss of HLA as a signal for activation. As efficient mediators of tumor immune surveillance and control, NK cells may be able to kill the cells many current immunotherapies leave behind. *Nersesian S et al. Front Immunol 2019;10:1782*

ANTICANCER RESEARCH *33*: 3855-3860 (2013)

Immunological Response after *WT1* mRNA-loaded Dendritic Cell Immunotherapy in Ovarian Carcinoma and Carcinosarcoma

AN COOSEMANS[1,5], ANKE VANDERSTRAETEN[2], SANDRA TUYAERTS[2], TINA VERSCHUERE[3], PHILIPPE MOERMAN[4,6], ZWI BERNEMAN[8], IGNACE VERGOTE[2,5], FRÉDÉRIC AMANT[2,5] and STEFAAN W. VAN GOOL[1,7]

Departments of [1]Microbiology and Immunology, [2]Gynecologic Oncology, [3]Neuroscience and [4]Imaging and Pathology, Katholieke Universiteit Leuven, Leuven, Belgium; [5]Gynecology and Obstetrics, [6]Pathology and [7]Pediatrics, University Hospital Leuven, Leuven, Belgium; [8]Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

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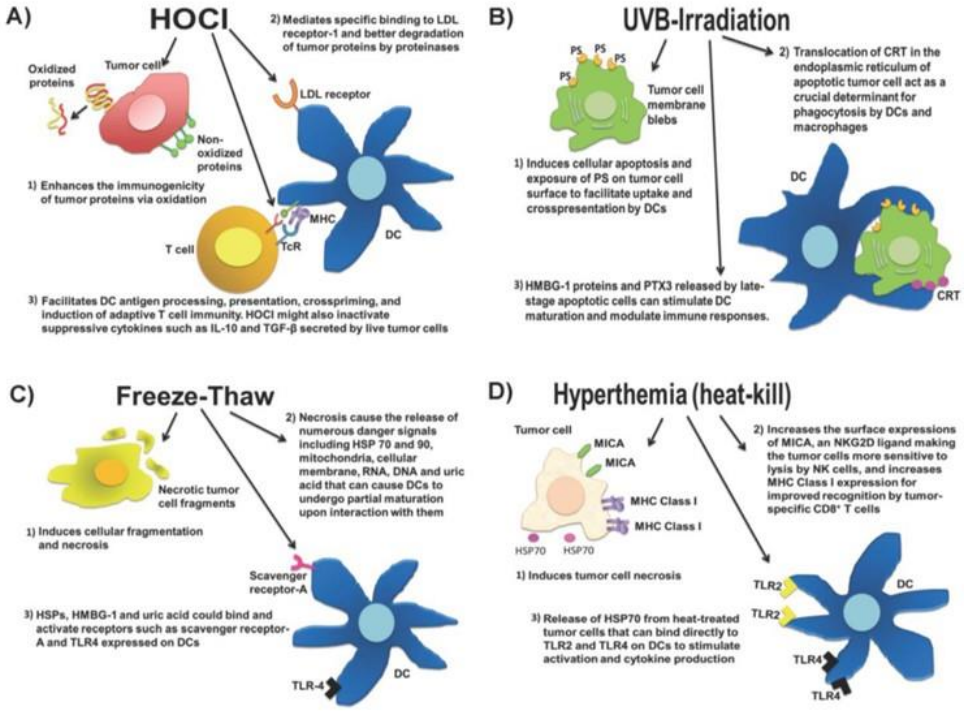

Figure 1. Four whole tumor lysate preparations currently in use in the clinics. (**A**)

Chiang CLL et al. Vaccines 2015;3:344-372

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IOZK GROUP 20190901

Wilfried Stuecker, Leitung der IOZK Arbeitsgruppe, Geschäftsführung

IOZK GmbH & Co.KG

Wilfried Stuecker

Praxis Stuecker &
Praxis Immun-onkologisches Zentrum Köln
Director: Stefaan Van Gool
Qualitätsbeauftragte: Jennifer Makalowski
Operations Manager: Mahmoud Wahidi

Medical team

Ärzte: Ahmed Boucharaba, Montassar Cherif, Karin Ehlert, Yadigar Genc, Bernhard Samirae
Medizinischer Gutachter: Tobias Sprenger (FB)
Data Manager: Marija Marko

Administrative team

Cécile Dürer (FB)
Katharina Auerbach, Ronny Sporbert, Ruken Durak, Funda Kurnaz

Nursing team

Margret Kubella, Julia Hupfer, Ute Graf, Nadine Herget, Julia Polecsak, Janos Kovacs, Martine Bauer, Julia Bauer

Cleaning

Emine Zayim

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Arbeitsanweisung **neue Version gültig ab 16.06.2019**

Stefaan Van Gool
Verantwortliche ärztl. Person

Material:

2 sterile Einmaltücher
1 Paar sterile Handschuhe
2 kleine sterile Tupfer
1 Butterflykanüle steril oder 1 Viggo steril
Monovetten je nach Alter des Patienten (siehe Tabelle 1)
Verwendet werden: EDTA-Monovette Fa Saarstedt/EDTA KE/9ml
Serum-Monovette Fa Saarstedt/Serum Gel /9 ml

Tabelle 1:

Alter	Anzahl EDTA-Monovetten	Anzahl Serum-Monovetten
Bis 6 Jahre	4-5	1
Bis 15 Jahre	10-15	1
Ab 16 Jahre/Erwachsene	23	1

Vorbereitung durch Personal in der Patientenbehandlung:

Überprüfung der Haltbarkeitsdaten des Materials. Entnahme der Röhrchen mit Handschuhen aus dem Originalgebinde und Legen der Röhrchen in eine Schale ausgeschlagen mit einem sterilen Einmaltuch (Tuch vorsichtig an den Ecken fassen und über die Schale breiten, Röhrchen einlegen). Keine weiteren Manipulationen.

Die Ärztin/der Arzt bereitet die Blutentnahme wie eine chirurgische Intervention vor:

Chirurgische Händedesinfektion
Sprühdesinfektion der Blutentnahmestelle, Tasten der Vene.
Sprühdesinfektion zentral über geplanter Blutentnahmestelle. Immer weg von der Punktionsstelle wischen, Tupfer direkt entsorgen
Sprühen und 1 min warten
Währenddessen steriles Einmaltuch auspacken, an den Ecken vorsichtig fassen und unter den Patientenarm legen
Anziehen von sterilen Handschuhen Nochmals Sprühen lassen durch Helferin Butterfly steril von Helferin anreichen lassen. Punktieren
Der Arzt entnimmt die Röhrchen mit seinen sterilen Handschuhen aus der mit dem sterilen Tuch ausgeschlagenen Schale und legt sie auch dorthin gefüllt zurück. Die Röhrchen werden nicht von anderen Händen angefasst.
Nach der Blutentnahme werden die Stempel durch den Arzt mit den sterilen Handschuhen abgebrochen und die Röhrchen mit den sterilen Handschuhen mit den Namensaufklebern beklebt. Dann werden die Röhrchen von dem Arzt mit den sterilen Handschuhen in das sterile Tuch in der Schale eingeschlagen und so mit Hilfe von Personal in der Patientenbehandlung möglichst „steril" in die Tüte verbracht. Ein Auspacken der Röhrchen erfolgt erst im Reinraumlabor.

Sollte eine Abweichung aus praktisch-klinischen Gründen von dieser Anweisung erfolgen, so soll dies auf der Blutabnahmedokumentation unter „Bemerkungen" vermerkt werden.

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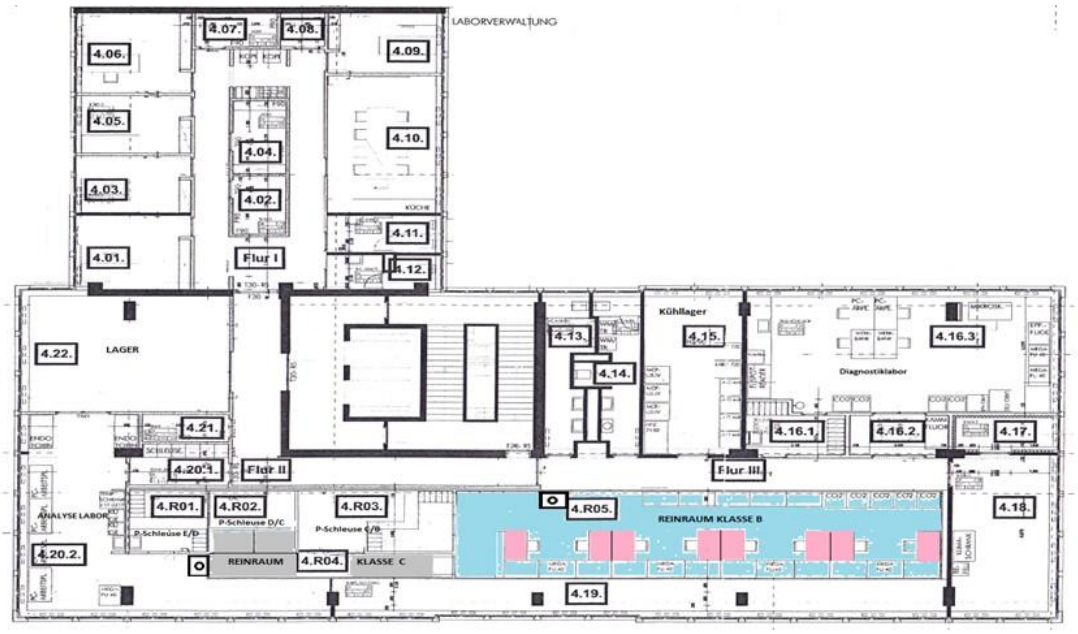
Flour 4 GMP



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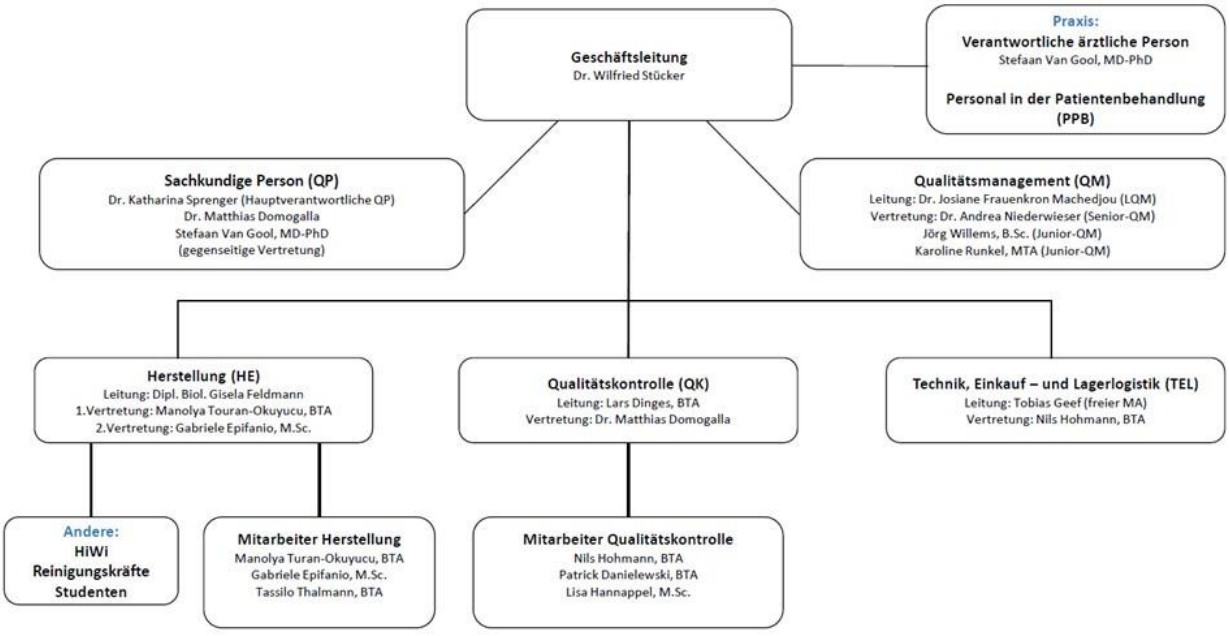
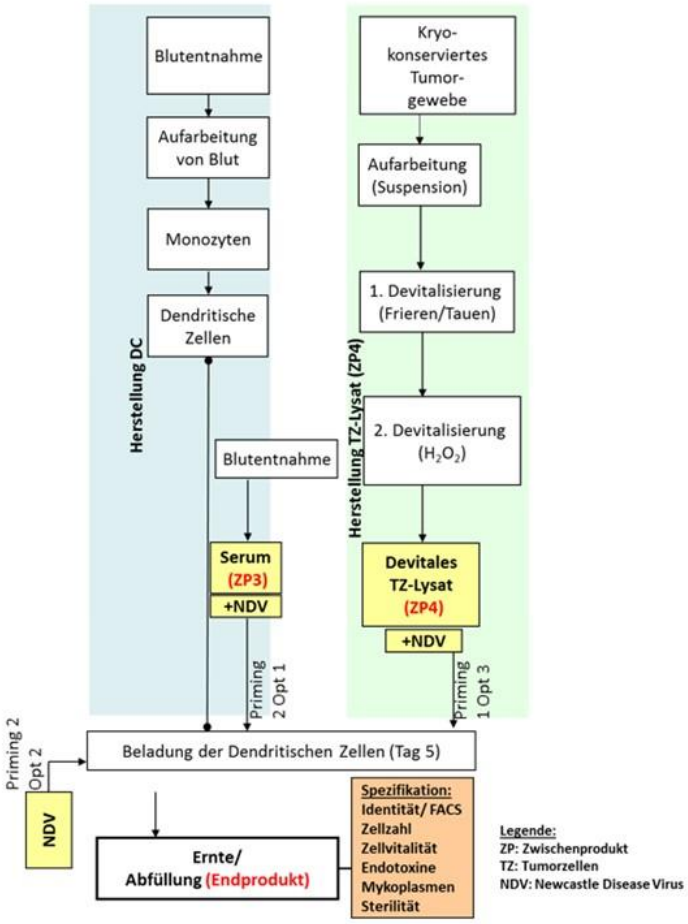
Flour 4 + 12 GMP





Legende:
ZP: Zwischenprodukt
TZ: Tumorzellen
NDV: Newcastle Disease Virus

Teil 2 | **Part 2**

- Humanarzneimittel
- Prüfpräparate zur Anwendung am Menschen der Phasen I, II, III

- Human Medicinal Products
- Human Investigational Medicinal Products for phase I,II,III

1 HERSTELLUNGSTÄTIGKEITEN

- Die erlaubten Herstellungstätigkeiten umfassen vollständige und teilweise Herstellung (einschließlich verschiedener Prozesse wie Umfüllen, Abpacken oder Kennzeichnen), Chargenfreigabe und -zertifizierung, Lagerung und Vertrieb der genannten Darreichungsformen sofern nicht anders angegeben;

- Die Qualitätskontrolle und/oder Freigabe und/oder Chargen-zertifizierung ohne Herstellungsschritte sollten unter den entsprechenden Punkten spezifiziert werden;

- Unter der relevanten Produktart und Darreichungsform sollte auch angegeben werden, wenn der Hersteller Produkte mit speziellen Anforderungen herstellt, z.B. radioaktive Arzneimittel oder Arzneimittel, die Penicilline, Sulfonamide, Zytostatika, Cephalosporine, Stoffe mit hormoneller Wirkung oder andere potenziell gefährliche Wirkstoffe enthalten (anwendbar für alle Bereiche des Teils 1 mit Ausnahme 1.5.2 und 1.6).

1 MANUFACTURING OPERATIONS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;

- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;

- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1	**Sterile Produkte**
	1.1.1 Aseptisch hergestellt
	1.1.1.4 Kleinvolumige flüssige Darreichungsformen
1.3	**Biologische Arzneimittel**
	1.3.1 Biologische Arzneimittel
	1.3.1.2 Immunologische Produkte
1.6	**Qualitätskontrolle**
	1.6.4 Biologisch

1.1	**Sterile Products**
	1.1.1 Aseptically prepared
	1.1.1.4 Small volume liquids
1.3	**Biological medicinal products**
	1.3.1 Biological medicinal products
	1.3.1.2 Immunological products
1.6	**Quality control testing**
	1.6.4 Biological

Einschränkungen oder klarstellende Anmerkungen betreffend den Umfang des Zertifikats:

Anmerkungen: zu 1.3.1.2
Spezifische, autologe Anti-Tumor-Dendritenzell-Vakzine zur intrakutanen Anwendung: -
aus Patienten-eigenen Monozyten gezüchtete dendritische Zellen, die mit Tumorantigenen aus einem Lysat patienteneigener Tumorzellen mit immunologisch wirksamen Gefahrensignalen ausgehend aus dem New Castle Disease Virus (NDV) beladen werden.

Any restrictions or clarifying remarks related to the scope of this certificate:

Comments: To 1.3.1.2
Specific, autologous anti-tumor directed dendritic cell vaccine for intracutaneous application:
from patient-derived blood monocytes generated dendritic cells which are loaded with tumor antigens from a lysate of patient-derived tumor cells together with immunologic danger signals from Newcastle disease virus (NDV).

DE_NW_04_GMP_2015_0030 27.05.2015

Bezirksregierung 170 Köln

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UMFANG DER ERLAUBNIS **Anlage 1**
Name und Anschrift der Betriebsstätte:
IOZK Laboratorium GmbH, Mauritiuswall 48, 50676 Köln

Humanarzneimittel

ERLAUBTE TÄTIGKEITEN
Herstellungstätigkeiten (gemäß Teil 1)

Teil 1 - HERSTELLUNGSTÄTIGKEITEN

- Die erlaubten Herstellungstätigkeiten umfassen vollständige und teilweise Herstellung (einschließlich verschiedener Prozesse wie Umfüllen, Abpacken oder Kennzeichnen), Chargenfreigabe und -zertifizierung, Lagerung und Vertrieb der genannten Darreichungsformen sofern nicht anders angegeben;

- Die Qualitätskontrolle und/oder Freigabe und/oder Chargenzertifizierung ohne Herstellungsschritte sollten unter den entsprechenden Punkten spezifiziert werden;

- Unter der relevanten Produktart und Darreichungsform sollte auch angegeben werden, wenn der Hersteller Produkte mit speziellen Anforderungen herstellt, z.B. radioaktive Arzneimittel oder Arzneimittel, die Penicilline, Sulfonamide, Zytostatika, Cephalosporine, Stoffe mit hormoneller Wirkung oder andere potenziell gefährliche Wirkstoffe enthalten (anwendbar für alle Bereiche des Teils 1 mit Ausnahme 1.5.2 und 1.6).

1.1	**Sterile Produkte**
	1.1.1 Aseptisch hergestellt
	1.1.1.4 Kleinvolumige flüssige Darreichungsformen
1.3	**Biologische Arzneimittel**
	1.3.1 Biologische Arzneimittel
	1.3.1.2 Immunologische Produkte
1.6	**Qualitätskontrolle**
	1.6.4 Biologisch

Einschränkungen oder Klarstellungen bezüglich der Herstellungstätigkeiten

zu 1.3.1.2
Spezifische, autologe Anti-Tumor-Dendritenzell-Vakzine zur intrakutanen Anwendung:
aus Patienten-eigenen Monozyten gezüchtete dendritische Zellen, die mit Tumorantigenen aus einem Lysat patienteneigener Tumorzellen mit immunologisch wirksamen Gefahrensignalen ausgehend aus dem New Castle Disease Virus (NDV) beladen werden.

IO-VAC®

DE_NW_04_IMA_2015_0033

Bezirksregierung 170 Köln

27.05.2015 10:27:00

Phase I/II clinical trial of modulated electro-hyperthermia treatment in patients with relapsed, refractory or progressive heavily treated ovarian cancer

IOZK | NEW PERSPECTIVES IN CANCER THERAPY

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Japanese Journal of Clinical Oncology 2019

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Abstract

Objective: To determine the maximal tolerated dose (MTD) of modulated electro-hyperthermia (mEHT) treatment and to reveal whether mEHT treatment is feasible and effective as second-line therapy in recurrent and progressive ovarian cancer.

Methods: Patients were treated with mEHT with dose escalation during the first cycle (two sessions each week for three weeks) to determine the MTD. Additional cycles were carried out with the determined dose. Dose limiting toxicity (DLT) was defined grade ≥ 2: skin burns and inability to endure the hyperthermic state of the study. The Fact-O quality of life scale was used to assess health-related well-being.

Results: Nineteen patients with recurrent and progressive ovarian cancer were enrolled. In the first cycle of mEHT treatment, no patient developed DLT with applied power up to 110 W, 130 W, and 150 W/day; the 150 W was the maximal applied power. Stable disease was observed in only one patient (12.5%). With median progression of 4.0 months (range, 2–17 months), 18 patients (95%) demonstrated disease progression. With median overall survival of 8.0 months (range, 2–32 months), 18 patients (95%) had died. Physical well-being scores were significantly decreased over the study period, although social, emotional, and functional well-being scores did not significantly change.

Conclusions: The mEHT treatment was feasible in patients with recurrent or progressive ovarian cancer without any complication and optimal dose of mEHT treatment was up to 150 W for 1 hour/day.

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biomedicines

MDPI

Review

Breaking Therapy Resistance: An Update on Oncolytic Newcastle Disease Virus for Improvements of Cancer Therapy

Volker Schirrmacher *, Stefaan van Gool and Wilfried Stuecker

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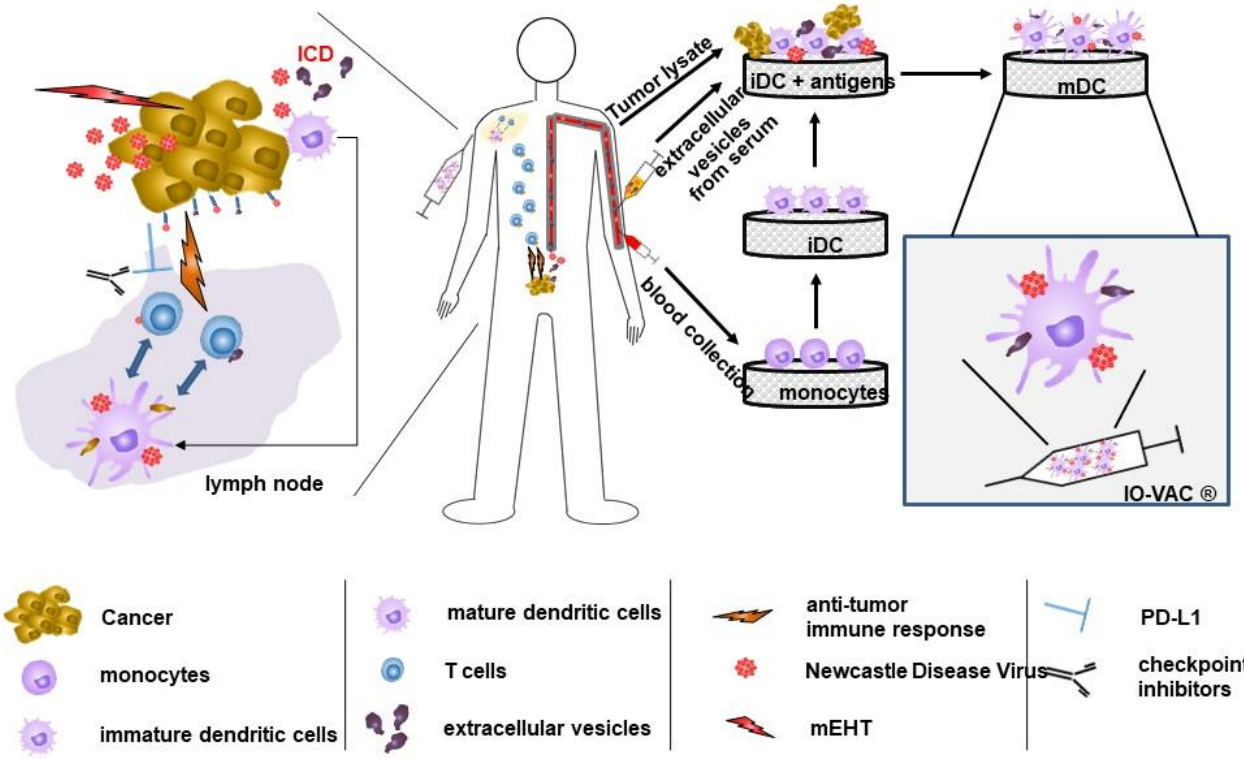
Received: 30 July 2019; Accepted: 23 August 2019; Published: 30 August 2019

Abstract: Resistance to therapy is a major obstacle to cancer treatment. It may exist from the beginning, or it may develop during therapy. The review focusses on oncolytic Newcastle disease virus (NDV) as a biological agent with potential to break therapy resistance. This avian virus combines, upon inoculation into non-permissive hosts such as human, 12 described anti-neoplastic effects with 11 described immune stimulatory properties. Fifty years of clinical application of NDV give witness to the high safety profile of this biological agent. In 2015, an important milestone was achieved, namely the successful production of NDV according to Good Manufacturing Practice (GMP). Based on this, IOZK in Cologne, Germany, obtained a GMP certificate for the production of a dendritic cell vaccine loaded with tumor antigens from a lysate of patient-derived tumor cells together with immunological danger signals from NDV for intracutaneous application. This update includes single case reports and retrospective analyses from patients treated at IOZK. The review also presents future perspectives, including the concept of in situ vaccination and the combination of NDV or other oncolytic viruses with checkpoint inhibitors.



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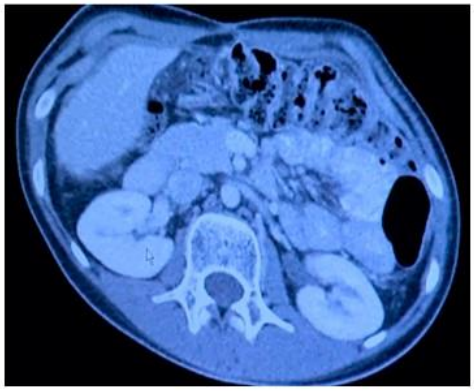
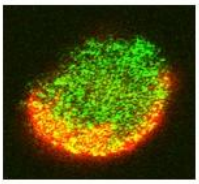


Translational oncology



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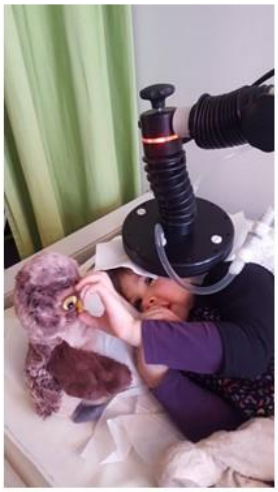

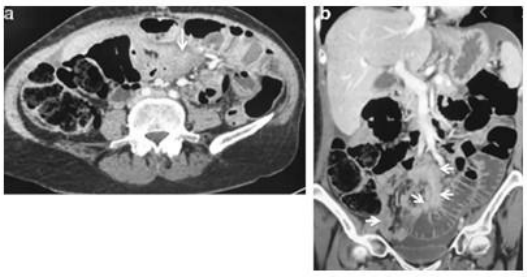

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Patient characteristics

Number	Age	Subtype	FIGO stadium	First line treatment	Second line treatment	Third line treatment	Fourth line treatment	Events prior to IO-VAC®
22657	48	Papillary	FIGO IV	S				1
22563	29	Mucinous	FIGO IA	S + S	S + CT + CT	S + HIPEC + CT	S + HIPEC	4
23125	37	Endometrioid	FIGO IIIC	S + CT	S + CT	CT	CT + Avastin	4
23232	58	Serous papillary	FIGO IV	CT + S				1
23359	38	Serous papillary	FIGO IIIC	R0 + CT	S + CT + Avastin	CT + Avastin		4
23529	64	Serous papillary	FIGO IIB	S + CT	B + CT			3
23597	48	Serous	FIGO IIIB	S + CT	S + HIPEC + CT			3
24009	38	Serous	FIGO IIIC	S + CT				2
24142	39	Serous papillary	FIGO IV	R1 + CT + Avastin	CT	TT	RCT	4

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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Immunotherapy details

Number	mEHT sessions	NDV injections	DC vaccination	DC cell numbers	Tumor antigens	TBH	Immuno-modulation	Other treatments
22657	43	43	4	43600000	MPs + Tumor-L + NDV	5	CPM	
22563	7	7	1	2550000	Tumor-L + NDV	1	CPM	
23125	17	17	0	0		2		
23232	25	25	2	24200000	MPs + Tumor-L + NDV	0		Avastin
23359	12	12	2	30600000	MPs + NDV	1		
23529	42	42	4	32200000	MPs + Tumor-L + NDV	2	ATRA	Avastin
23597	21	21	2	17000000	MPs + NDV	2	ATRA	
24009	15	15	2	19800000	MPs + NDV	0	ATRA	
24142	12	12	2	45200000	MPs + NDV	5	ATRA	

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

Overall survival

Number	Age	Subtype	FIGO stadium	Events prior to IO-VAC®	OS since diagnosis (months)	OS since IO-VAC® treatment (months)
22657	48	Papillary	FIGO IV	1	**+ 43,9**	+ 39,38
22563	29	Mucinous	FIGO IA	4	37,21	3,48
23125	37	Endometrioid	FIGO IIIC	4	**+ 144,63**	31,93
23232	58	Serous papillary	FIGO IV	1	12,2	6,69
23359	38	Serous papillary	FIGO IIIC	4	69,25	1,54
23529	64	Serous papillary	FIGO IIB	3	74,49	10,92
23597	48	Serous	FIGO IIIB	3	**+ 57,87**	+ 18
24009	38	Serous	FIGO IIIC	2	**+ 29,21**	+ 7,25
24142	39	Serous papillary	FIGO IV	4	**+ 48,82**	+ 2,75

*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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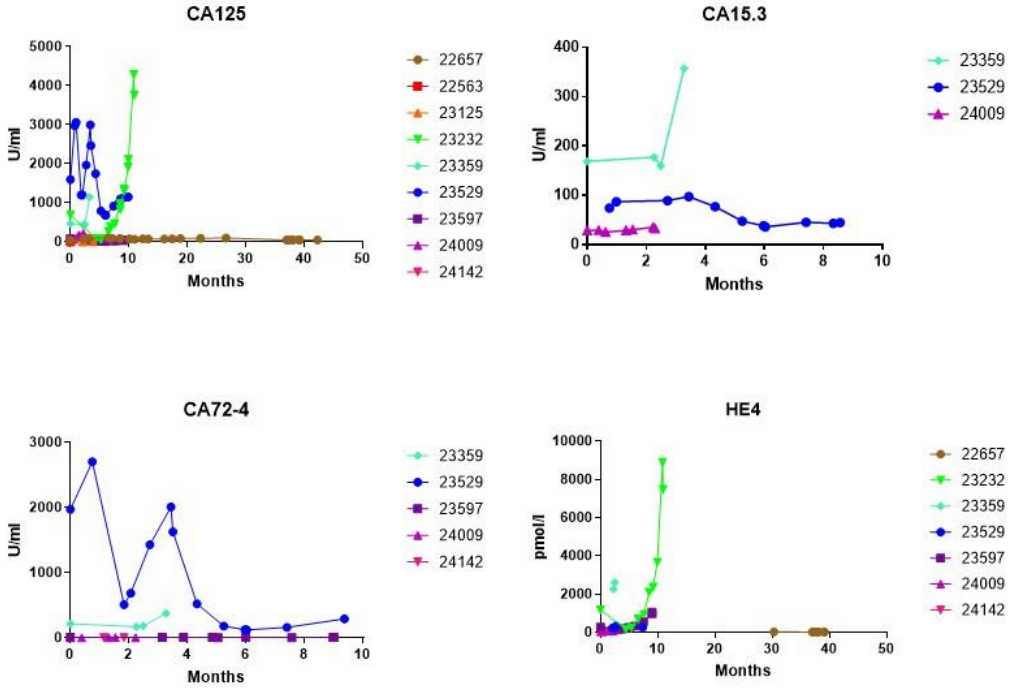
Tumor markers



*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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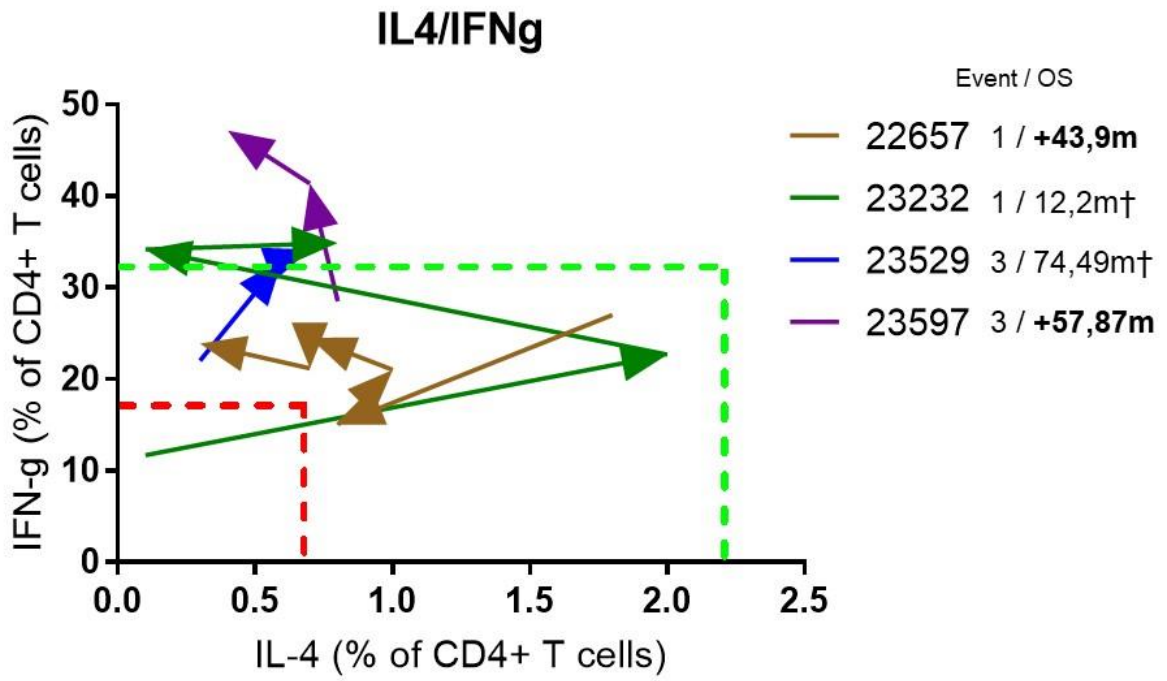
Th1 / Th2 balance



*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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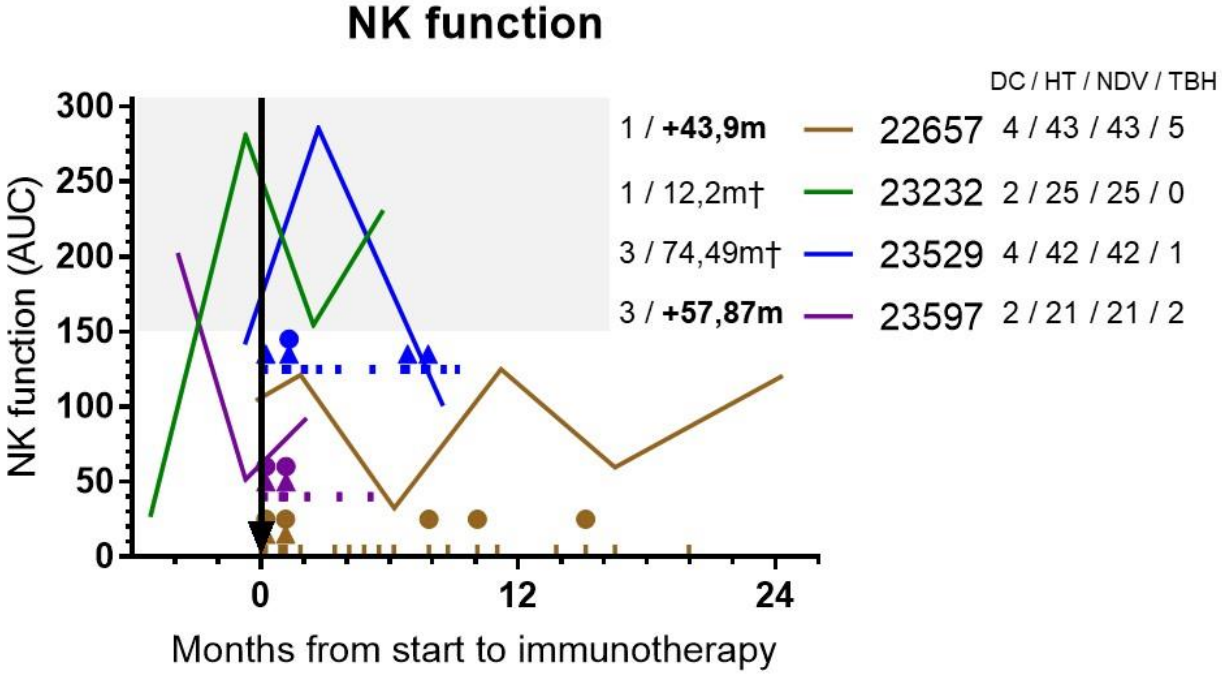
NK cell function



*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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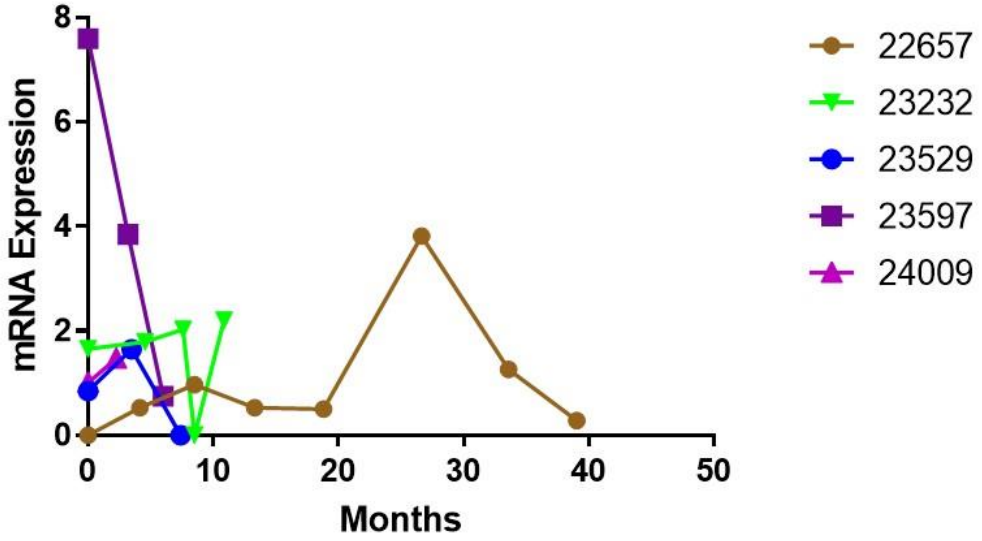
Messenger RNA expression for PDL1 on Circulating Cancer Cells



*Retrospective summary of patients treated as „**Individueller Heilversuch**“*

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Conclusion

- Multimodal immunotherapy for ovarian cancer
  - NDV injections
  - Modulated electrohyperthermia sessions
  - Autologous DC vaccines loaded with autologous tumor antigens
  - Immunomodulatory strategies
    - Total body hyperthermia
    - Checkpoint inhibitors
    - Others
- Ambulant treatment, feasible without major toxicities
- OS might be prolonged with good quality of life

Numerical Simulation and Evaluation of Magnetic Particle Hyperthermia System and Conditions

Nikos Maniotis and Theodoros Samaras

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E-mail: nimaniot@physics.auth.gr

Presented at the 37th ICHS, Thessaloniki

Cite this article as:

Maniotis N. and Samaras T. (2019): Numerical Simulation and Evaluation of Magnetic Particle Hyperthermia System and Conditions, Oncothermia Journal 27: 153- 161
www.oncotherm.com/sites/oncotherm/files/2019-10/Numerical_Simulation.pdf

Introduction
Magnetic particle hyperthermia (MPH) is a novel, minimally invasive, therapeutic modality, used as a cancer treatment, that employs a magnetic fluid (also termed ferrofluid) as the heating source. A magnetic fluid is a stable colloidal suspension of magnetic nanoparticles (MNPs) that can be injected directly into the tumor or delivered to the tumor via passive or active targeting upon intravenous administration. Once accumulated to the tumor area, MNPs are exposed to an external alternating magnetic field (AMF) that causes reversal of their magnetic moments, activating mechanisms of energy deposition in the form of heat [1].

Objectives
The main objective of the present work is the development and evaluation of numerical models for the description of the phenomena that take place in a MPH *in vitro* system. In particular, we aim at the estimation of the spatial distribution of the magnetic field and the spatiotemporal temperature distribution by taking into account all the appropriate field and heat transfer boundary conditions.

Material/Methods
In order to simulate the physical phenomena, two numerical models were developed in COMSOL Multiphysics. In the first model the "Azimuthal Induction Currents" interface provided in "AC/DC" Module, was used in order to obtain the magnetic field distribution corresponding to a 2-turn circular and 8-turn squared coil geometries, while in the second model the transient analysis of the "General Heat Transfer" interface provided in "Heat Transfer" Module was employed to calculate the MNPs volumetric power dissipation (by importing Rosensweig's model [2]) and obtain the time-dependent heating curves. The ferrofluid concentration used was 4 mg/ml for an aqueous solution of 10 nm magnetite MNPs, dispersed in 1 ml of water, while the AMF amplitude and frequency were 30 mT and 765 kHz, respectively, for the 2-turn coil, and 60 mT and 365 kHz, respectively, for the 8-turn coil.

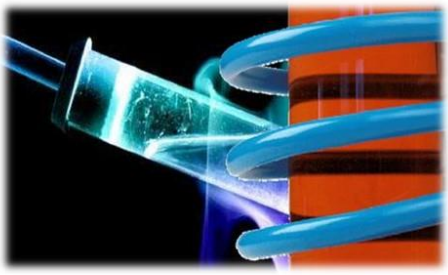
Results
The solution of the electromagnetic problem provides the magnetic field distribution for the experimentally applied current amplitude and frequency. The role of coils geometry is also presented since COMSOL takes into account the coil geometrical characteristics, ignored in the analytical expressions. Moreover, the solution of the Heat Transfer problem gives the spatial distribution of temperature in the various subdomains of the MPH system like the ferrofluid, the vial, the coil and the surrounding air while the time-dependent heating curves are obtained after 30 minutes of treatment and are compared to the corresponding experimental ones observed under the same conditions. The spatiotemporal distribution of the MNPs volumetric power dissipation is also estimated for the non-adiabatic conditions, studied in the present work, validating Rosensweig's model [2].

Conclusion
Proper use of simulations can lead to better understanding of complex physical processes, further progress in the development of novel MPH equipment designs, replacement of invasive temperature measurements and establishment of updated hyperthermia treatment protocols. In silico testing and evaluation of material properties and innovative methods can substantially accelerate their approval for clinical use and result in better treatment quality.

References
[1] Dutz, S. and Hergt, R. (2014) Magnetic particle hyperthermia—a promising tumour therapy?. Nanotechnology., 25(45), 452001.

[2] Rosensweig, R. E. (2002) Heating magnetic fluid with alternating magnetic field. J. Magn. Magn. Mater., 252,370-374.

NUMERICAL SIMULATION AND EVALUATION OF MAGNETIC PARTICLE HYPERTHERMIA SYSTEM AND CONDITIONS



N. Maniotis and T. Samaras
MagnaCharta Group, Physics Department, Aristotle University of Thessaloniki, Greece

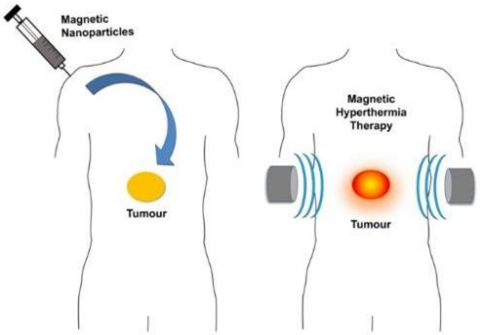
37th Conference of the International Clinical Hyperthermia Society

INTRODUCTION

NUMERICAL SIMULATION AND EVALUATION OF MAGNETIC PARTICLE HYPERTHERMIA SYSTEM AND CONDITIONS

Introduction

MAGNETIC PARTICLE HYPERTHERMIA



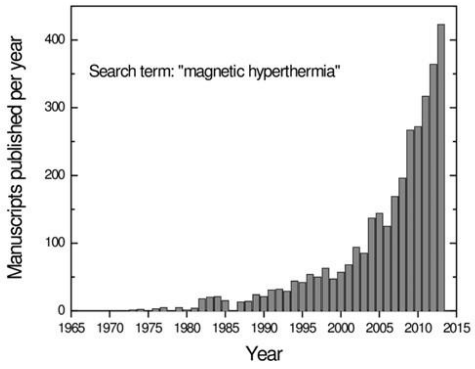
- Magnetic particle hyperthermia: novel, **minimally invasive**, therapeutic modality, used as a **cancer treatment**, that employs a **magnetic fluid** (also termed ferrofluid) as the **heating source**.
- Magnetic fluid: stable colloidal suspension of **magnetic nanoparticles** injected **directly** or delivered to the tumor via passive or active (functionalized) targeting upon **intravenous** administration.
- Nanoparticles: tiny particles of **iron oxide** suspended - very finely distributed - in **water**. As soon as applied, they **agglomerate** and remain like an **implant** in the tissue to be treated.
- Alternating magnetic field causes the particles to generate **heat**.

✓ Cancer cells more **susceptible** than healthy at **41-45°C temperature region**, **rise** within this **region** leads to **suppression** of cancer cells growth and tumor **shrinkage.**

Nikos Maniotis, Physics Department, AUTH

Introduction

MAGNETIC PARTICLE HYPERTHERMIA



Applied Physics Reviews 2.4, 041302 (2015)

- 1957: Was first proposed by Gilchrist et. al.
- 2011: MagForce (Berlin, Germany). obtained the first and only European Union regulatory approval of a nanotechnology therapy for treatment of brain tumors.

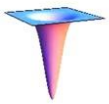
- NanoTherm® therapy combines the use of a ferrofluid (i.e. aqueous SPIONs), which is injected directly into the tumor site, and an AMF applicator, which is set to operate at a fixed frequency, of 100 kHz with an amplitude range, from 2 to 15 kA/m.
- Magnetic hyperthermia is used as an adjuvant therapy to RT and ChT.

Nikos Maniotis, Physics Department, AUTH

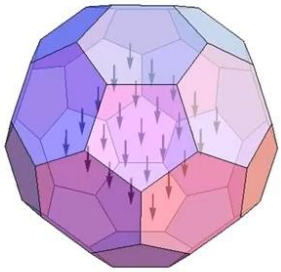
Introduction

PHYSICAL MECHANISMS OF POWER DISSIPATION IN THE TISSUE ENVIRONMENT

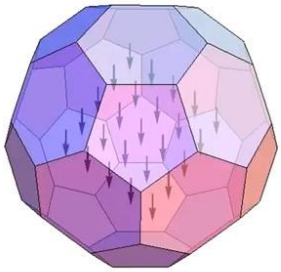
- When an external magnetic field that provides sufficient energy is applied to the system, the magnetic moment of a nanoparticle may be displaced from its preferred orientation. Consequently, as the magnetic moment returns to the equilibrium state (relaxation), thermal energy is released.



AMF



Néel relaxation



Brown relaxation

Rosensweig's model (Adiabatic system)

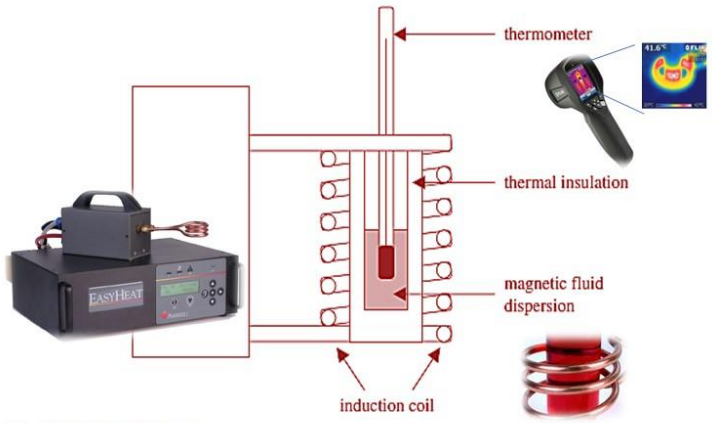
$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2} \quad [W/m^3]$$

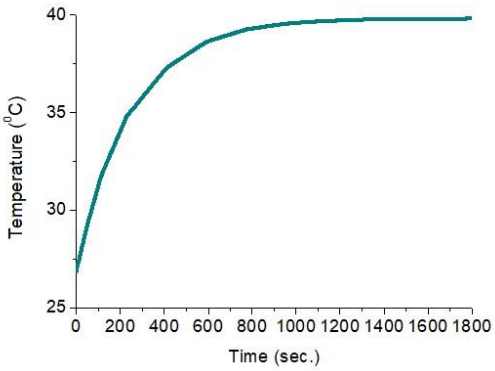
Introduction

IN VITRO TESTING

Frequency: 100-1000 kHz

Magnetic Filed Intensity Amplitude: 10-100 kA/m





- The main objective of the present work is the development and evaluation of numerical models for the description of the phenomena that take place in a MPH in vitro system.

PROCEDURE & CONDITIONS

- In order to simulate the physical phenomena, two numerical models were developed in COMSOL Multiphysics v. 3.5a.

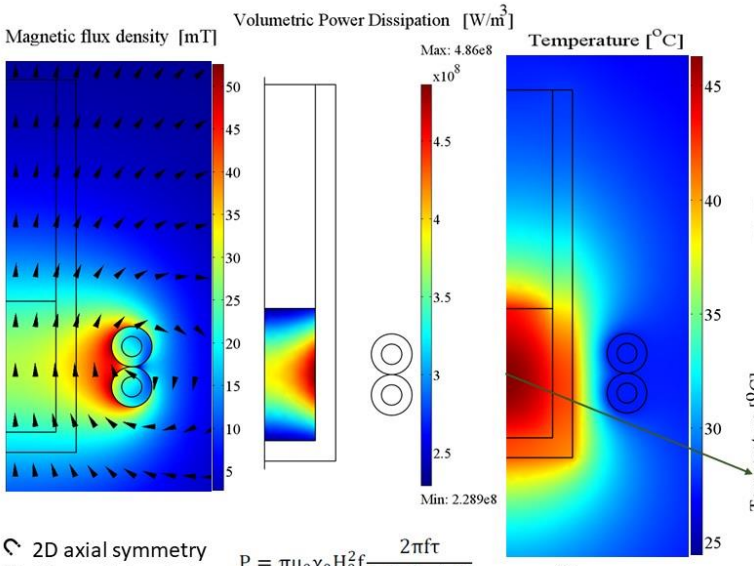
Parameters examined

- Effect of coil geometry
- Boundary conditions
- Time-dependent heating curves
- Nanoparticles distribution in ferrofluid
- Efficiency

- ✓ Amplitude : 30 mT, 60 mT
- ✓ Frequency : 765 kHz, 400 kHz
- ✓ Magnetic Nanoparticles diameter : 10 nm
- ✓ Material: Magnetite (Fe_3O_4)
- ✓ Concentration: 4 mg/mL
- ✓ Solution: 1 mL Water
- ✓ Volume fraction (φ): 0.07%

Methods and Results

2-TURN CIRCULAR COIL



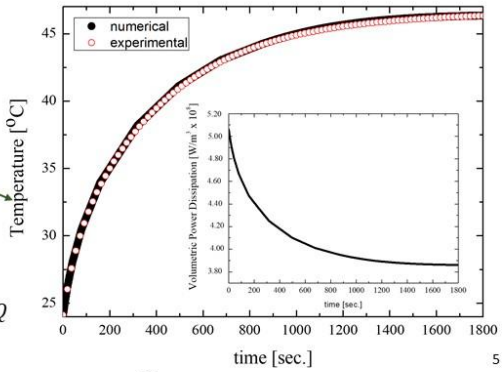
- 2D axial symmetry
- Magnetic Insulation
- Continuity

$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2}$$

$$\rho C_p \frac{\partial T}{\partial t} + \nabla \cdot (-k\nabla T) = Q$$

$$Q = P \times \varphi$$

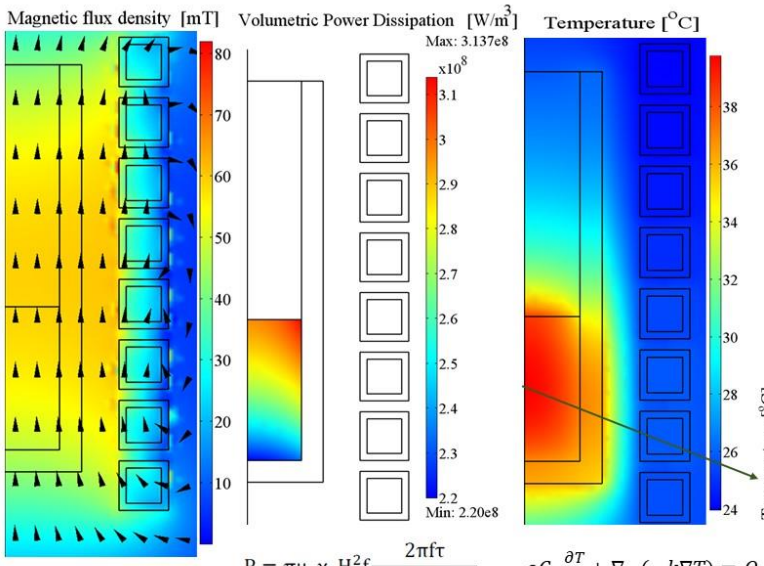
- 2D axial symmetry
- Convective Heat Flux (Natural and Forced)
- Radiation
  - i. surface to surface
  - ii. surface to ambient
- Dirichlet



5

Methods and Results

8-TURN SQUARED COIL



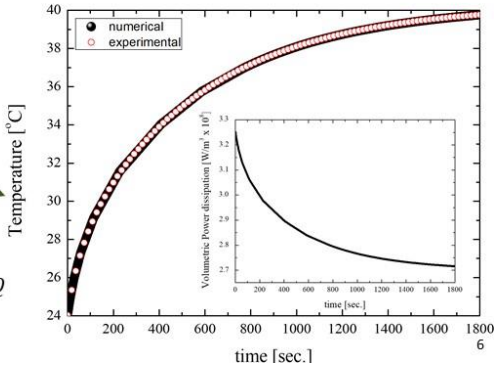
- 2D axial symmetry
- Magnetic Insulation
- Continuity

$$P = \pi\mu_0\chi_0 H_0^2 f \frac{2\pi f\tau}{1+(2\pi f\tau)^2}$$

$$\rho C_p \frac{\partial T}{\partial t} + \nabla \cdot (-k\nabla T) = Q$$

$$Q = P \times \varphi$$

- 2D axial symmetry
- Convective Heat Flux (Natural and Forced)
- Radiation
  - i. surface to surface
  - ii. surface to ambient
- Dirichlet



6

CONCLUSIONS

- The role of coils geometry in field homogeneity is presented since COMSOL takes into account the coil geometrical characteristics, ignored in the analytical expressions.
- The time-dependent heating curves are in good agreement with the corresponding experimental ones observed under the same conditions validating our method.
- The assumption of nanoparticles homogeneous spatial distribution in the water was also verified by the good agreement between theoretical and experimental results.
- The appropriate dose is chosen so as not to attenuate magnetic nanoparticles thermal performance but also to be absorbed to the maximum possible from the tissues and yield the best possible heat.
- Proper use of simulations can lead to better understanding of complex physical processes, further progress in the development of novel MPH equipment designs, replacement of invasive temperature measurements and establishment of updated hyperthermia treatment protocols.
- In silico testing and evaluation of material properties and innovative methods could substantially accelerate their approval for clinical use and result to better treatment quality.

ICHS 37th Conference of the International Clinical Hyperthermia Society

Nikos Maniotis, Physics Department, AUTH

7

THE MAGNACHARTA GROUP

Physics Department, Aristotle University of Thessaloniki

Magnetic **Na**nostructure **Char**acterization: **T**echnology and **A**pplications

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- **Post doc Researchers**

Despoina Sakelari, Kostas Simeonidis, Antonis Makridis

- **PhD Students**

Eirini Myrovali, Aikaterini-Rafailia Tsiapla, Antonia-Areti Kalimeri

THANK YOU FOR YOUR ATTENTION

This work has been supported by the State Scholarships Foundation (IKY)

ICHS 37

Nikos Maniotis, Physics Department, AUTH

The effects of microwave normothermic irradiation on cultured cancer cells

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Presented at the 37th ICHS, Thessaloniki

Cite this article as:

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www.oncotherm.com/sites/oncotherm/files/2019-10/The_effect_of_microwave.pdf

Introduction

Microwaves (frequency: 0.3–300 GHz) have long been used in cancer therapies such as microwave coagulation therapy and hyperthermia therapy. In these therapies, microwave irradiation is used to kill tumour cells by raising cellular temperature. These therapies have been used for treatment of various cancers for a long time. In recent years, microwave irradiation technology has been developed further, and it has been reported that the yield and reaction rate of many chemical reactions can be increased by microwave irradiation at a much lower temperature as compared to a conventional heating method such as water bath heating[1]. Therefore, we hypothesized that microwave normothermic irradiation might affect biological phenomena in cells.

Objectives

We previously developed a microwave irradiation system that could irradiate cells under normothermic conditions by controlling the outputs and frequency precisely[2]. We then investigated the cell death pathways in HL-60 cells, induced during microwave irradiation under normothermic conditions. After being exposed to our microwave irradiation system, the cells were killed through "caspase-independent apoptosis"[3]. In this study, we investigated the cell death of other cultured cancer cells by microwave irradiation such as T98G (for human glioblastoma cells), MDA-MB-231 (for human breast cancer cells), and KATO III (for human gastric cancer cells).

Material/Methods

T98G, MDA-MB-231, and KATO III cells were seeded in 35 mm culture dishes containing 2.5 mL of media, at a density of 1×10^5 cells/mL. Microwave irradiation (2.45 GHz) was applied for 1h, and the temperature of cells was maintained at 37 °C. However, the temperature inside the applicator, during these experiments, was set at 10 °C. Following irradiation, the cells were moved to a CO_2 incubator, where they were incubated for 6 h before used in the following assays; Caspase 3/7 assay carried out by using Caspase-3/7 Assay Kit (AnaSpec, San Jose, CA, USA) and Annexin V-PI assay performed by using an Annexin V-FITC Apoptosis Detection Kit (Nacalai Tesque).

Results

According to the microscopic observations, the number of late stage apoptotic cells (both Annexin V and PI positive) had increased in all cell types, while early apoptotic cells (Annexin V positive, PI negative) were not observed. The adherent cell types, T98G and MDA-MB-231, were cast off by microwave irradiation, further indicating that cells were near death. Moreover, after microwave irradiation, the activity of caspase 3/7 did not increase significantly in any of the cell types.

Conclusion

The results indicate that cell death pathways activated by microwave irradiation in the examined cells may be similar. However, further investigations should be performed to better understand the effects of irradiation on each cell type in detail.

References

[1] Sawada T. and Yamada T. (2018) J. Jpn. Petrol. Inst., 61(2), 121-128.

[2] Asano M., Sakaguchi M., Tanaka S., et al. (2017) Effects of normothermic conditioned microwave irradiation on cultured cells using an irradiation system with semiconductor oscillator and thermo-regulatory applicator, Sci Rep, 7, 41244.

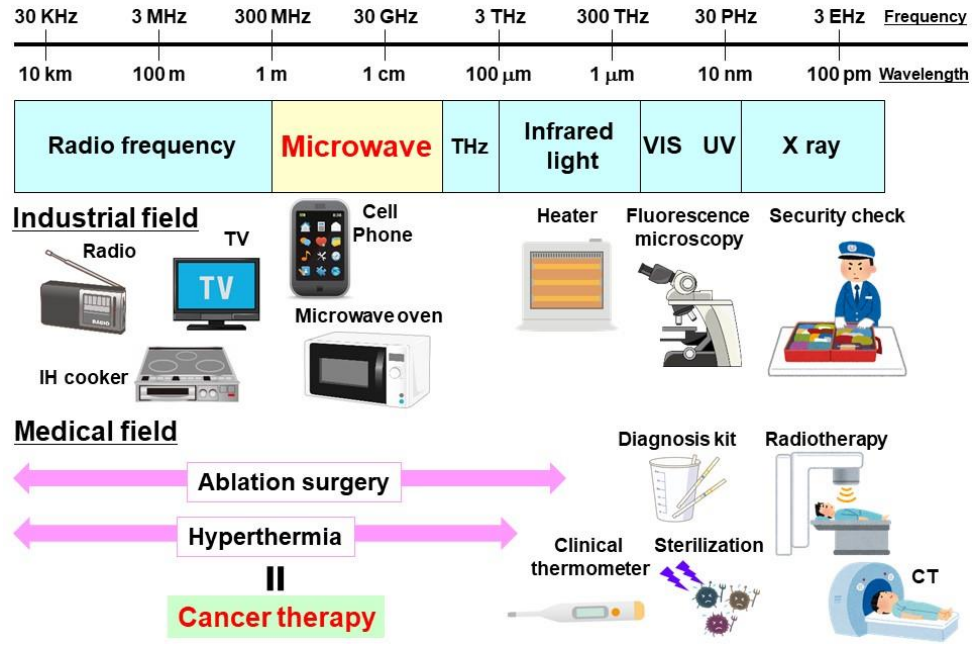
[3] Asano M., Tanaka S., Sakaguchi M., et al. (2017) Normothermic microwave irradiation induces death of HL-60 cells through heat-independent apoptosis. Sci Rep, 7(1), 11406.

The Effects of microwave normothermic irradiation on cultured cancer cells

Mamiko Asano[1], Minoru Sakaguchi[2], Satoshi Tanaka[2]

[1]Research Institute for Sustainable Humanosphere, Kyoto University, Japan.
[2]Osaka University of Pharmaceutical Sciences, Japan.

What are 'Microwaves'?



Outline of our presentation

Recent trends of microwave irradiation
- Spread of a semiconductor oscillator
- Development of simulation technology for electromagnetic field

We can control microwave energy for cells precisely.

Outline
1, Microwave irradiation system for cultured cells.

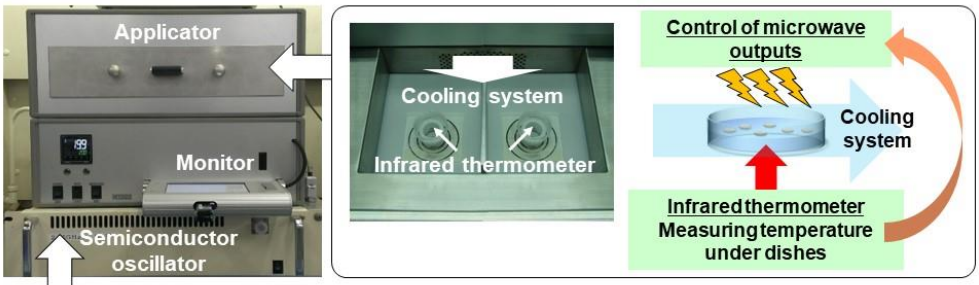
2, Cell death pathway by microwave normothermic irradiation.

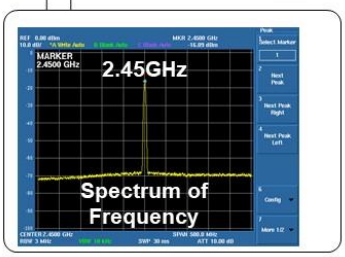
*normothermic: at normal body temperature

Microwave irradiation system

Microwave can be irradiated normothermically* in this system

*normothermal: at normal body temperature





Specifications
- Model number: MTS03(S)
  (Made by Sunny Engineering Co. Ltd.)
- Frequency: 2.45 GHz
- Outputs: 0-40 W
- Temperature in applicator: 10-45°C

Procedure: assays of cell death pathways

HL-60 cells (Human promyelocytic leukemia cells)
1×10^5 cells/mL

Negative control group
Without any treatments

Microwave irradiation group
Kept at 37°C for 1 h
(Applicator: 10°C)

Thermal treatment group
Incubation at 42.5°C for 1 h
(Most of cells are killed at 42.5°C.)

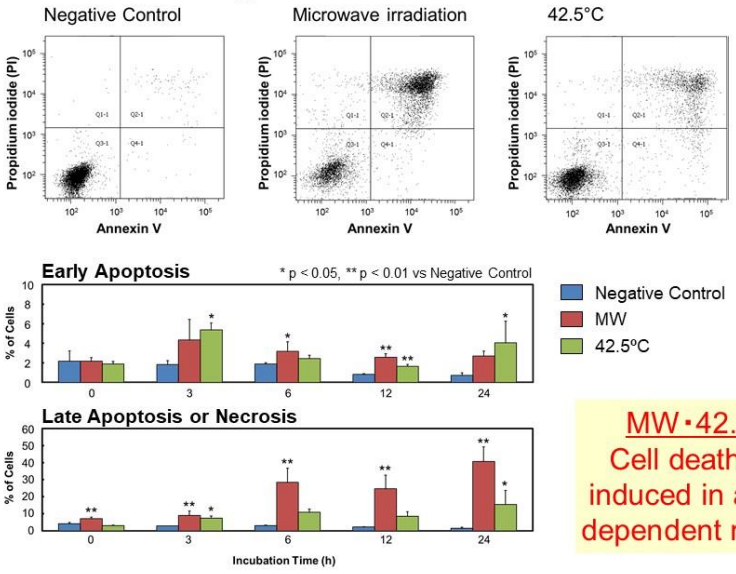
Incubation in CO_2 incubator for 0-24 h

Assays of cell death pathways
(Western blotting, ELISA assay, microscope observation, etc.)

Annexin V - Propidium Iodide (PI) assay

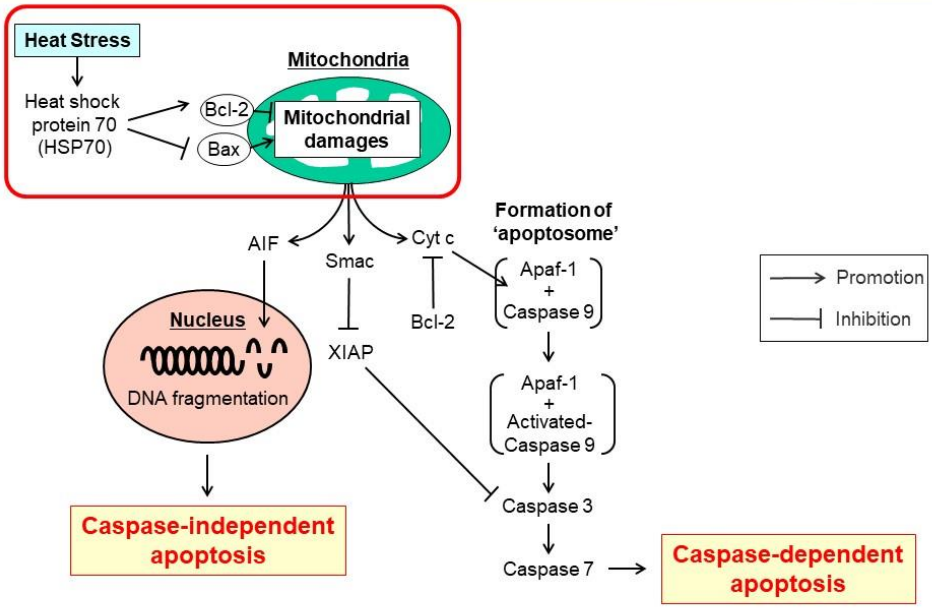
Asano M* et. al., *Sci. Rep.*, 7, 11406 (2017).

After 24 h following treatments



MW・42.5°C
Cell death was induced in a time-dependent manner.

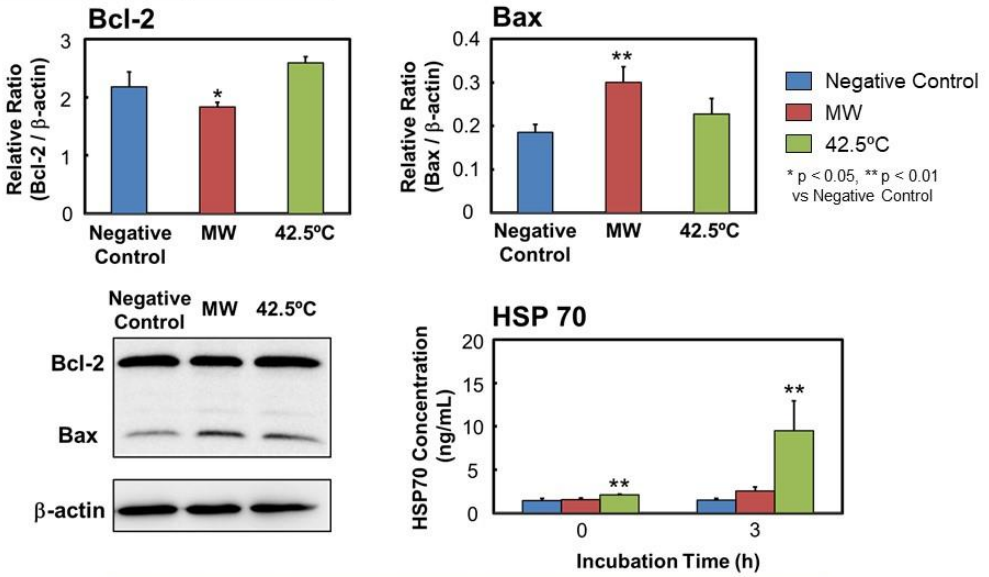
Caspases-related apoptotic pathways



Expression of Bcl-2 family and HSP 70 activation

After 3 h following treatments

Asano M* et. al., *Sci. Rep.*, 7, 11406 (2017).

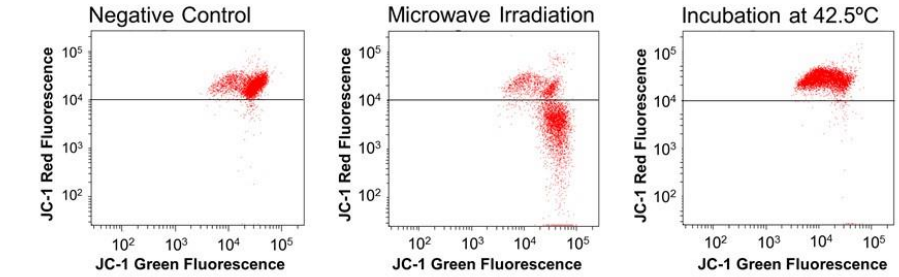


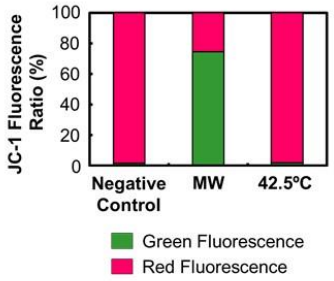
MW Bcl-2 family promoted mitochondrial damages.
42.5°C Thermal stress response was occurred.

Mitochondrial membrane potential (Δψm) assay

Asano M* et. al., *Sci. Rep.*, 7, 11406 (2017).

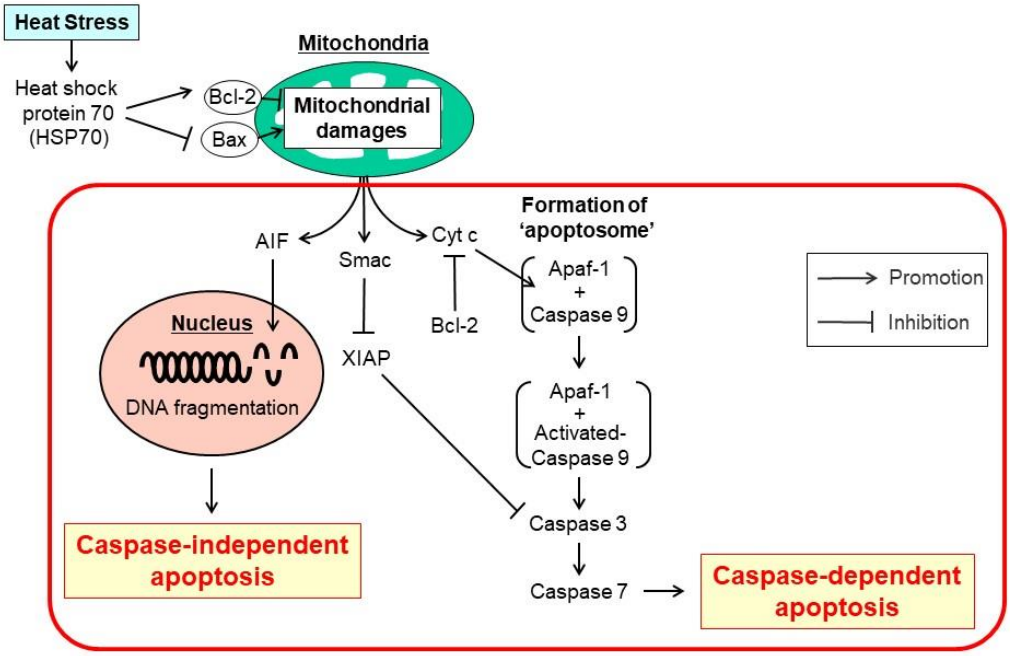
After 3 h following treatments





MW
Mitochondria was damaged.
42.5°C
No effect on Δψm

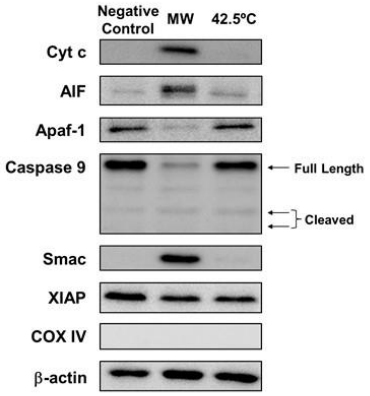
Caspases-related apoptotic pathways

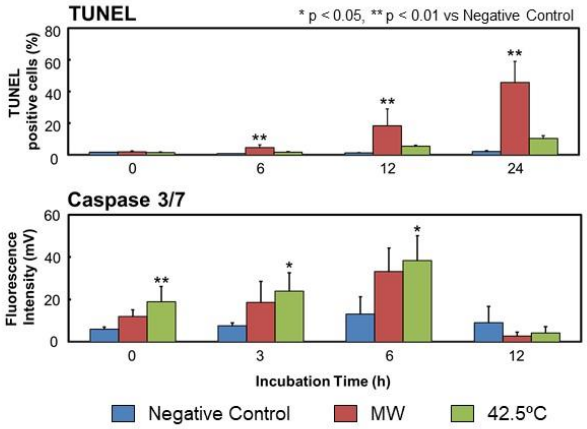


Caspase independent or dependent apoptosis

Asano M* et. al., *Sci. Rep.*, 7, 11406 (2017).

After 3 h following treatments (Cytosol extraction)

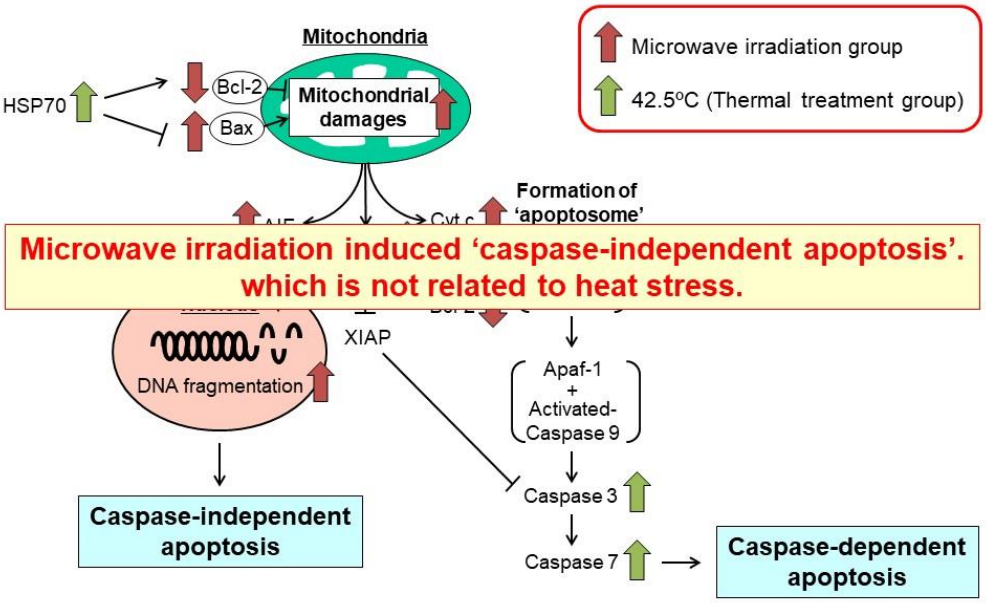




MW
AIF induced DNA fragmentation.
⇒Caspase independent apoptosis

Summary: apoptotic cell death pathways

*Asano M et. al., *Sci. Rep.*, 7, 11406 (2017).



Procedure: cell death assays

1×10^5 cells/mL

- T98G cells (Human glioblastoma multiforma tumor)
- MDA-MB-231 cells (Human breast adenocarcinoma)
- KATO III cells (Human gastric carcinoma)

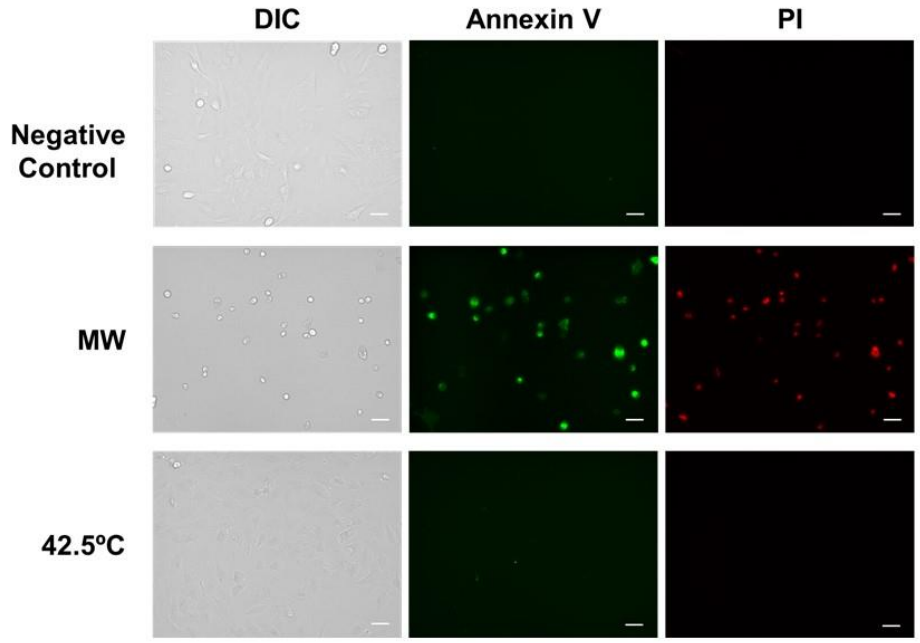
Negative control group	Microwave irradiation group	Thermal treatment group
Without any treatments	Kept at 37°C for 1 h (Applicator: 10°C)	Incubation at 42.5°C for 1 h (Most of cells are killed at 42.5°C.)

Incubation in CO_2 incubator for 0-24 h

Cell death assays
(Annexin V-PI assay, Caspase 3/7)

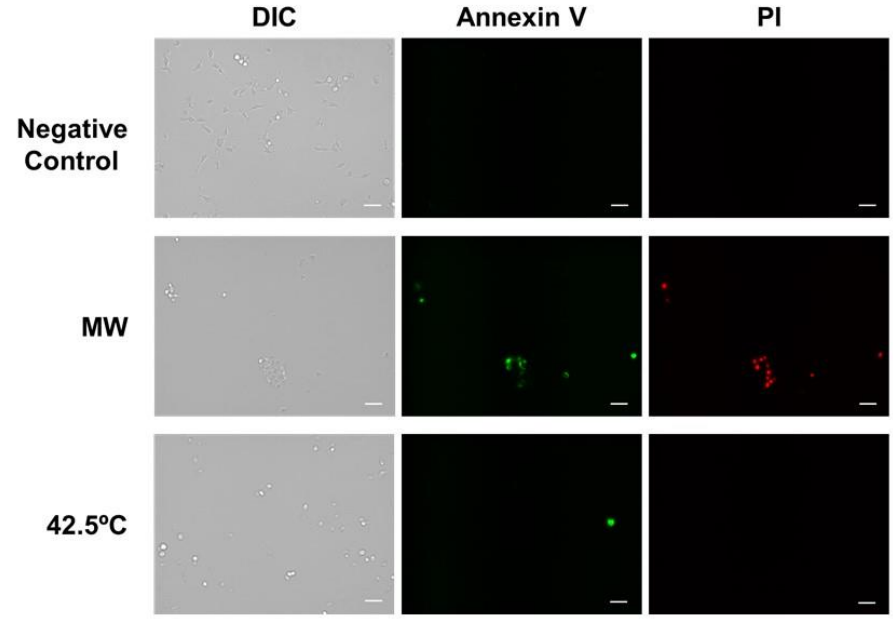
Annexin V-PI assay (T98G)

T98G



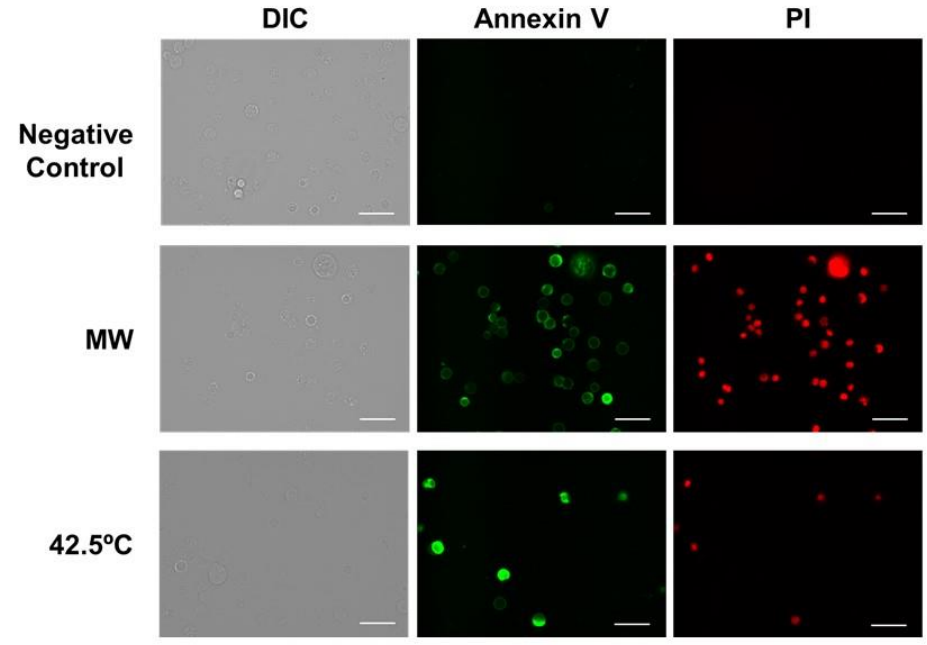
Annexin V-PI assay (MDA-MB-231)

MDA-MB-231



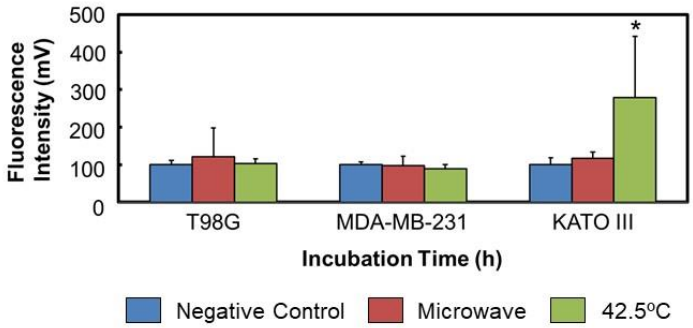
Annexin V-PI assay (KATO III)

KATO III



Caspase 3/7 assay

Caspase 3/7



Caspase 3/7 was…
- NOT activated by microwave irradiation.
- activated in KATO III cells only at 42.5°C.

Conclusion

Microwave irradiation

- HL-60 cells were killed through 'Caspase **independent** apoptosis'.
- T98G, MDA-MB-231 and KATO III cells might be killed through the similar pathway of HL-60 cells.

42.5°C (Thermal treatment group)

- Cells were killed through 'Caspase **dependent** apoptosis' .

Future works
- Cell death analysis for many types of cancer cells.
- Application to *in vivo* (e.g. xenograft mouse models).

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Thank you for your attention!

Evaluation of clinical studies when no reference arm exists

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www.oncotherm.com/sites/oncotherm/files/2019-10/Evaluation_of_clinical_studies.pdf

In the advanced metastatic stages of the malignant diseases the standard curative therapies usually fail, and the patient receive palliative care only. In the case of modulated electro-hyperthermia (mEHT, tradename oncothermia) this situation is common. The patients come to mEHT when no other curative therapy is available, and mEHT tries to turn the simple palliation to the curative therapeutic approach again. This could be with resensitization of the standard conventional therapies or applied mEHT in monotherapy regime together with the best supportive care. The treatment setup in these cases is very individual, it depends on the previous treatments and their results, the reason of the inapplicability of conventional methods (like organ failure, hemato-complications, refractory status, intolerable side effects, comorbidities, etc.). Due to the broad spectra of the patients and the missing availability of other active treatment for comparison form randomized, the double arm is impossible.

Furthermore, sometimes highly personalized therapies combined with mEHT block the collection of the homogeneous group and limit its double-arm randomization. Due to the above problems, many clinical trials have prospective or retrospective datasets without comparison to the control-group formed by the same cohort as the active one. The measured single arm naturally contains the relevant information; however, in most of the cases, it is impossible to obtain it from the complex survival curve without a reference. Our objective is to discuss the situations of the single arm evaluation. We give a method for the mining of information from single arm study to increase the level of evidence of the measured dataset. The basic idea of the data-separation is the appropriate parameterization of the non-parametric Kaplan-Meier survival pattern by the psychometric poly-Weibull fit. With the Weibull decomposition of the survival curve, we can fit at least two subgroups of patients. The weighted sum of the decomposed fractions could be optimized analytically and determining the best parameters of the components and the best composition ratio of the weighted sum is also possible. We will show how the method works in a real clinical environment through mEHT as a complementary method, applied curatively when no other conventional curative therapies are available. The decomposed function of the non-responding group provides an excellent agreement with the historical controls in the investigated group of patients with pancreatic cancer and non-small-cell-lung-cancer studies.

37th Conference of
International Clinical Hyperthermia Society
Thessaloniki Greece, September 19-21, 2019

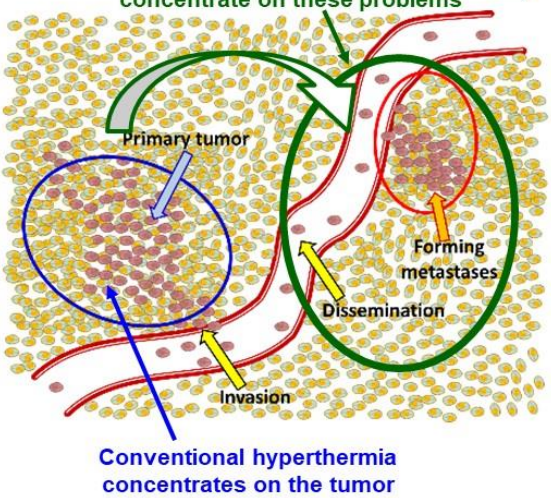
Evaluation of clinical studies, when reference arm doesn't exist

Andras Szasz, Ph.D.
Professor, St. Istvan University
CSO of Oncotherm Group

Outline

- ❑ The problem of the evidences in advanced diseases
- ❑ The general behaviour of the survival curves
- ❑ The strategies of studies
- ❑ Evaluation examples: pancreas, lung, glioblastoma

Challenge of hyperthermia in oncology



The challenge of evidence based statistical evaluation:

patients are **heavily pretreated**, having large variety of advanced stages with metastases, relapses

⇩

they are in fact in the **palliative** phase only

⇩

no cohort can be collected

⇩

prospective or retrospective single arm study can be only constructed

How to deal with this challenge?

Outline

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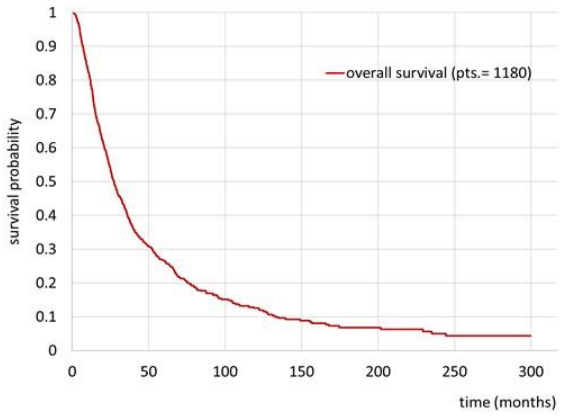
The survival curve

Well-known **Kaplan-Meier** non-parametric estimation shows survival probability by time



Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and practices. Springer Science, Heidelberg

The Kaplan-Meier estimate contains **all relevant information,** only we are **not able to filter it** (missing reference)

The survival has special self-similar behavior, because the **step-wise** growing of the tumor.

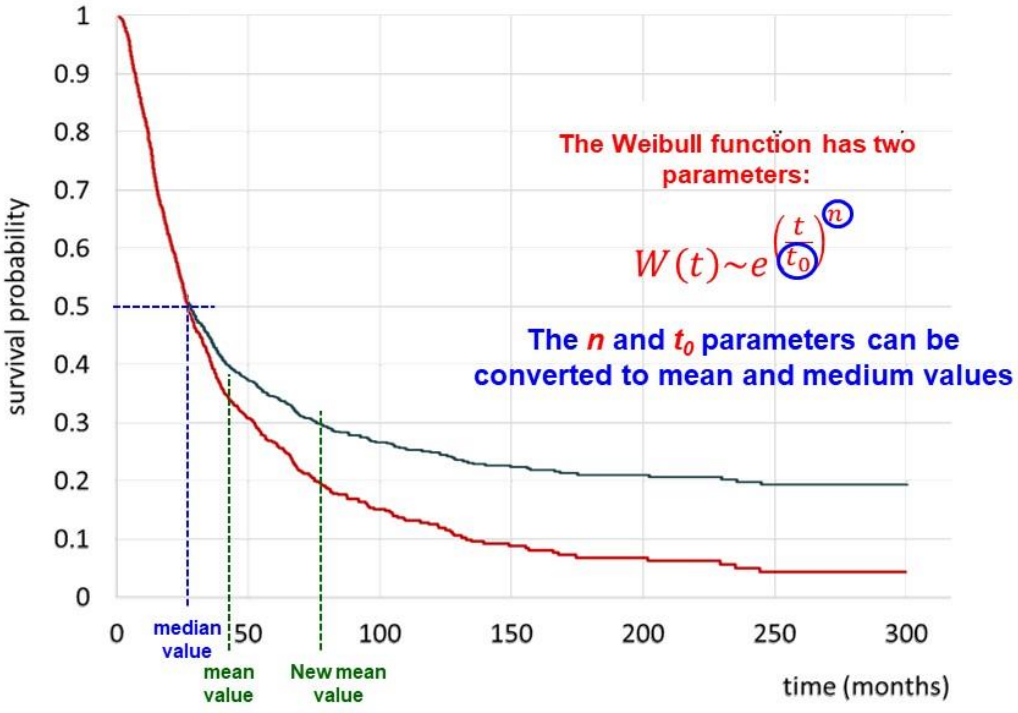
All new cells met the condition of the **microenvironments** produced by the cells in previous steps

The **self-similar** development could be followed by the physiologic-psychologic function:
Weibull-function

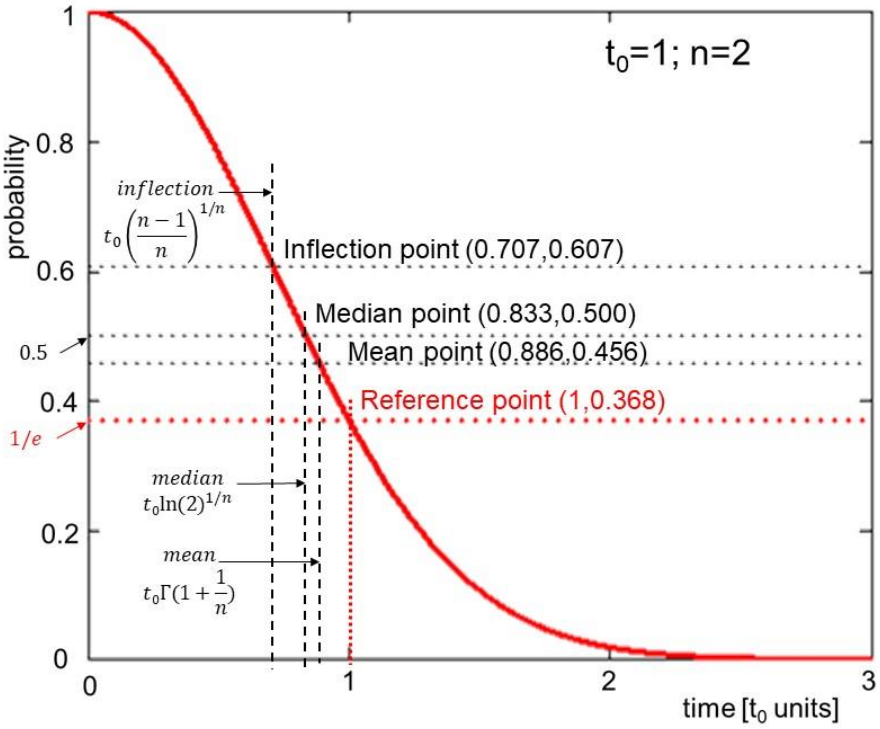
$$W(t) \sim e^{\left(\frac{t}{t_0}\right)^n}$$

where t is the time, t_0 is a scale factor and n is a form factor

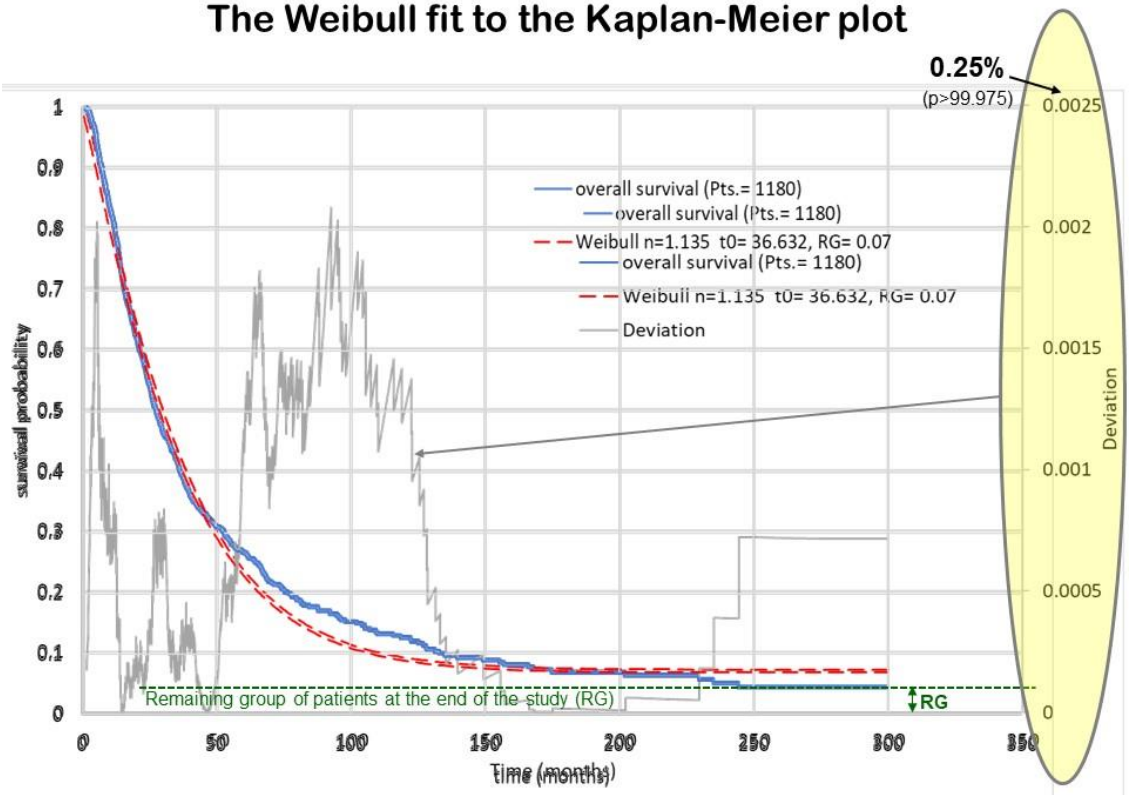
Two parameters characterize the survival curve



The Weibull function

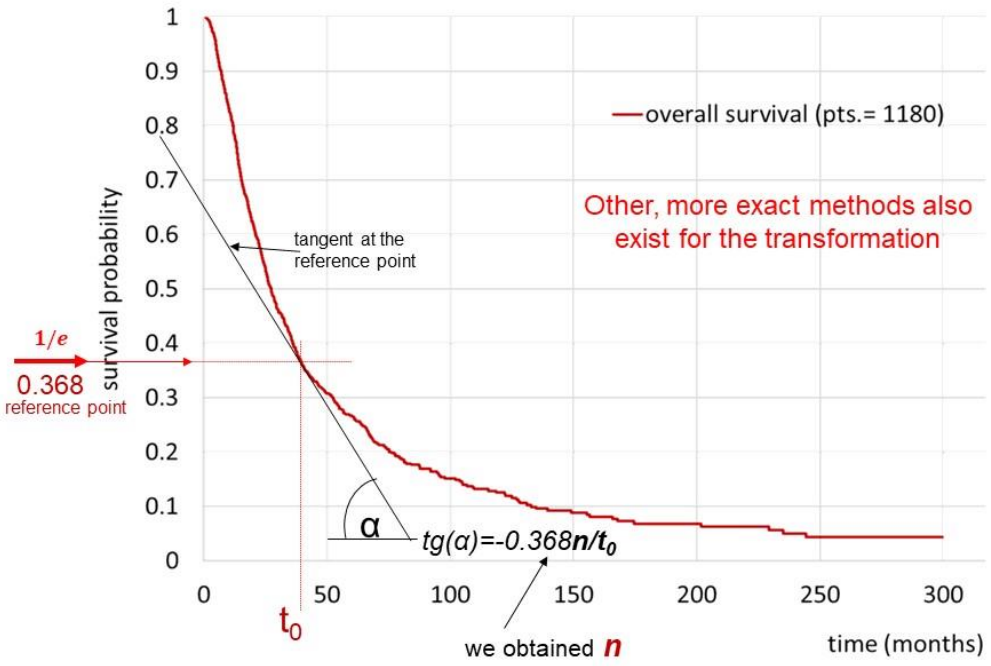


The Weibull fit to the Kaplan-Meier plot



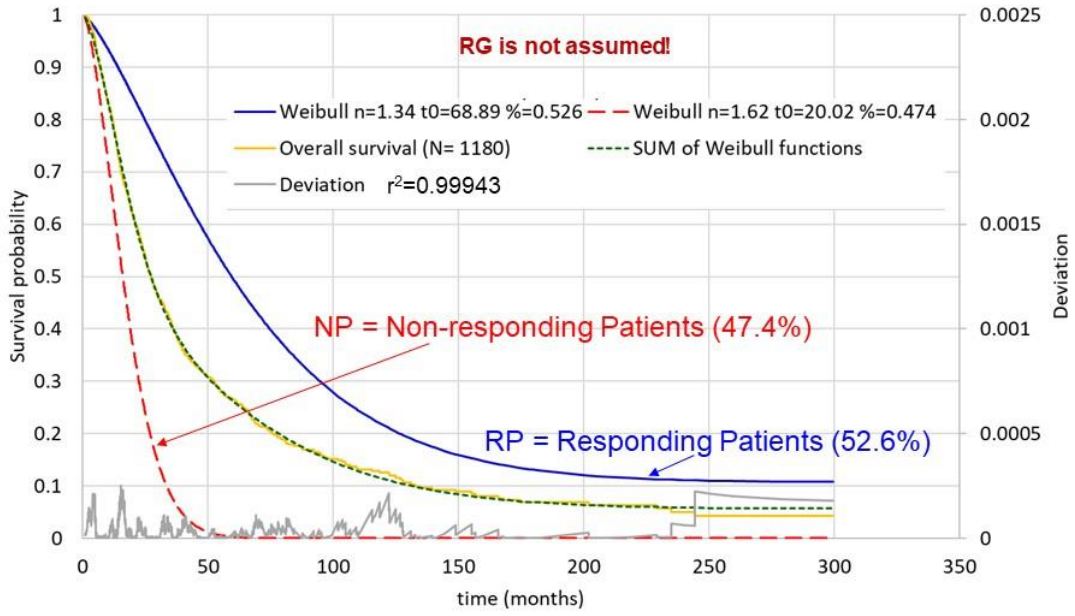
Two parameter conversion in the survival curve

Two parameters, mean and median could be transferred to ***n*** and t_0



Calculating responding and non-responding patients

$$W^{(KM)}(t) = c_{RP}e^{-\left(\frac{t}{t_0^{(RP)}}\right)^{n^{(RP)}}} + (1-c_{RP})e^{-\left(\frac{t}{t_0^{(NP)}}\right)^{n^{(NP)}}}$$



Outline

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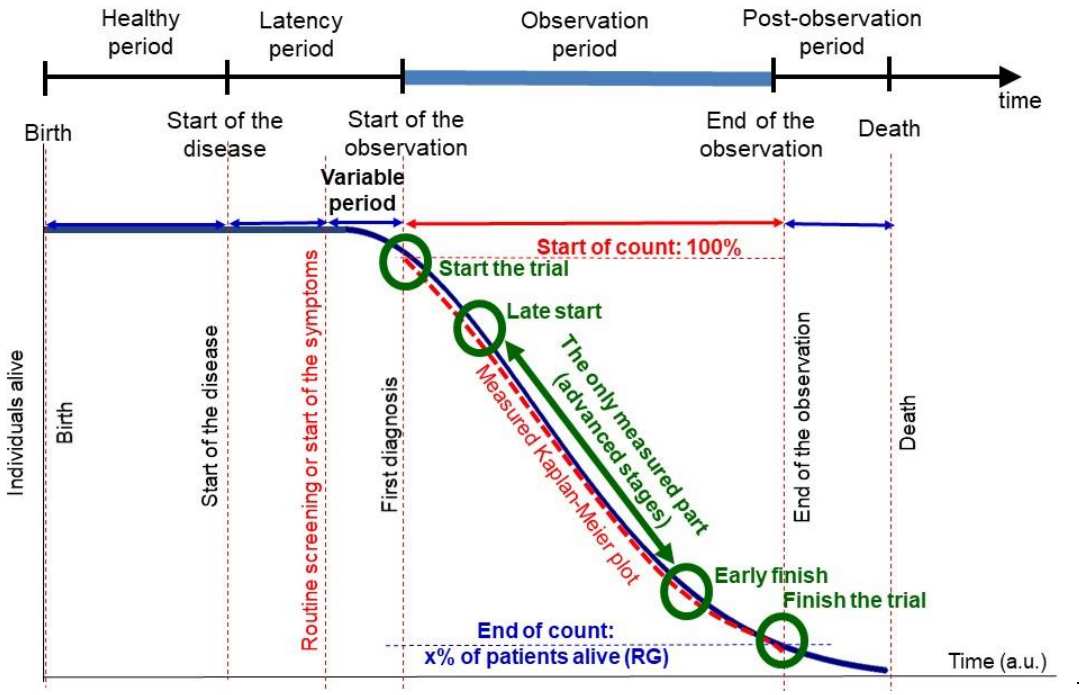
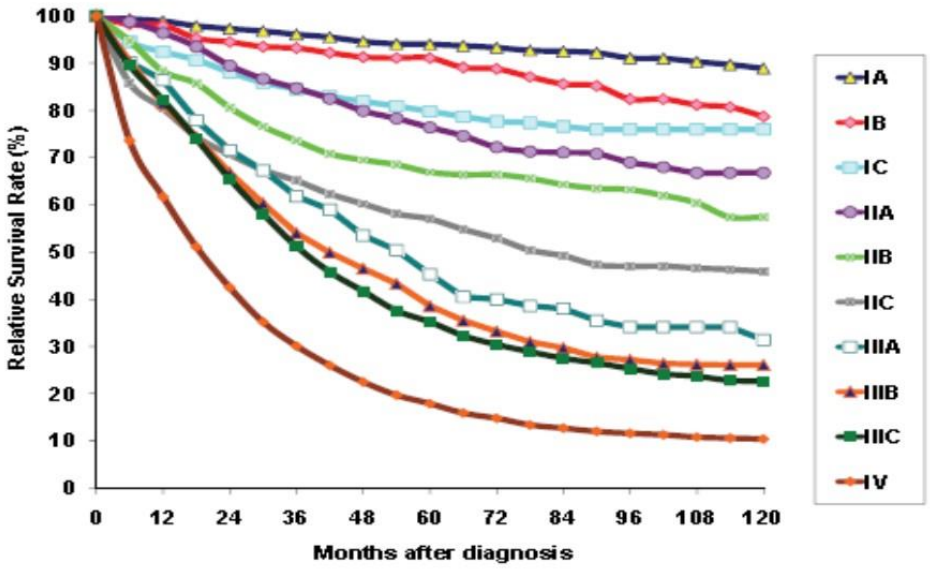
Complete life-span of the patient

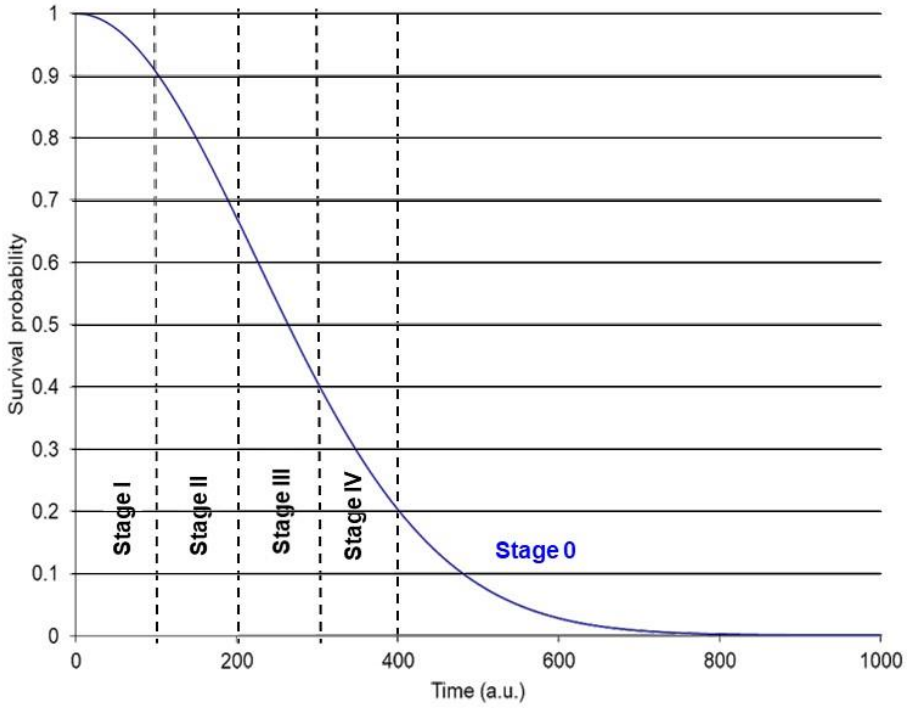


Trials for advanced stages (NSCLC)

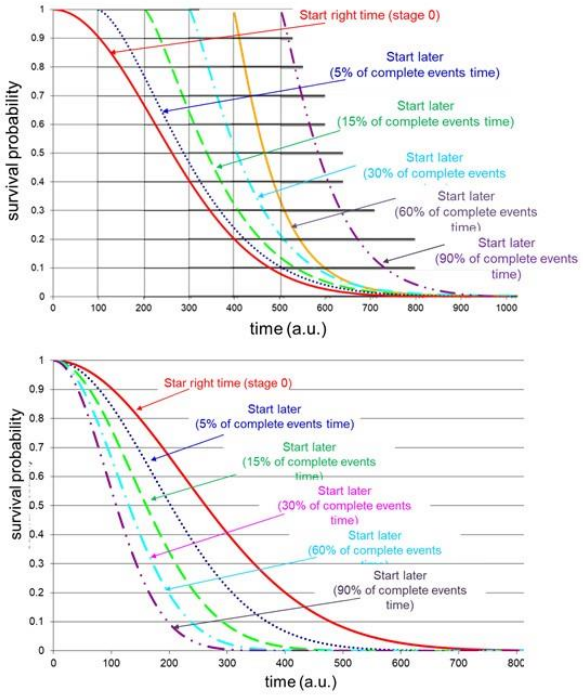


Late start challenge

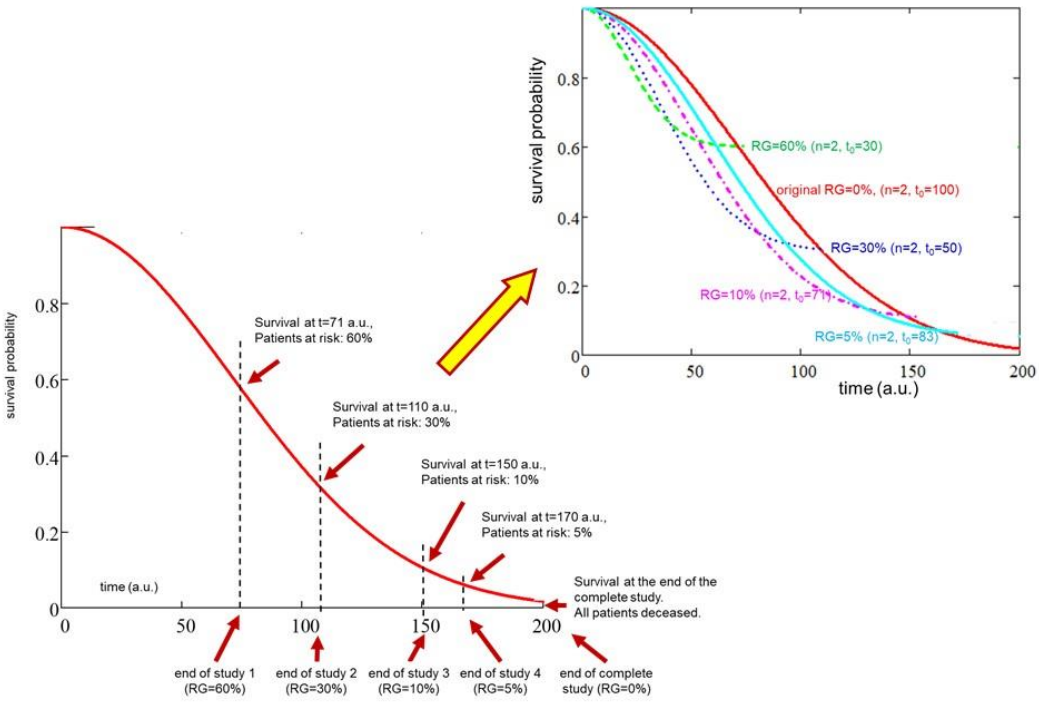
All late starts consider their start point as 100%, and starts at zero time



Consider every late start as 100%



The early end situation truncates the original plot



Outline

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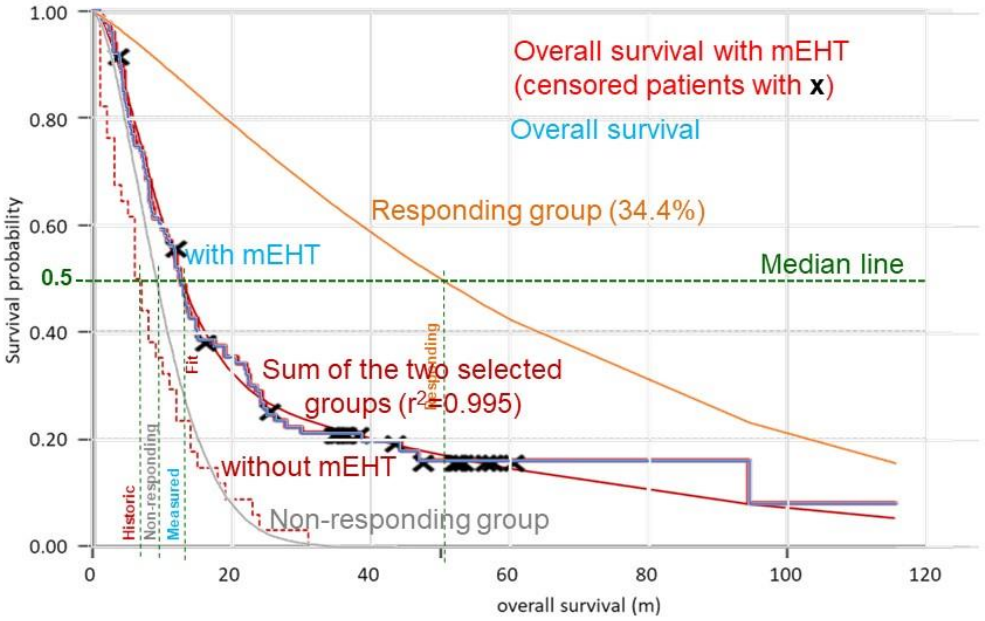
Study of inoperable advanced pancreas carcinoma

Dani A, et al. (2008) Clinical study for advanced pancreas cancer treated by oncothermia. Forum Hyperthermie 1:13–20

Number of patients
- active arm n=99 (73+26 two centers)
- control arm n=34 (historical control)

Decomposition to responding and non-responding groups

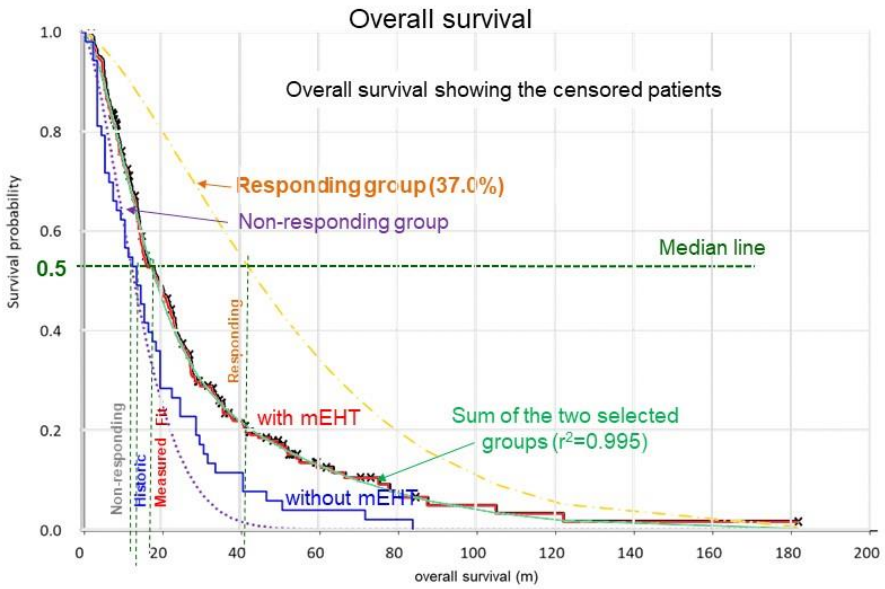


Study of advanced non-small-cell lung cancer

Szasz A (2014) Current status of oncothermia therapy for lung cancer. Korean J Thorac Cardiovasc Surg 47:77-93

Number of patients
- active arm n=258 (197+61 two centers)
- control arm n=53 (historical control)

Decomposition to responding and non-responding groups

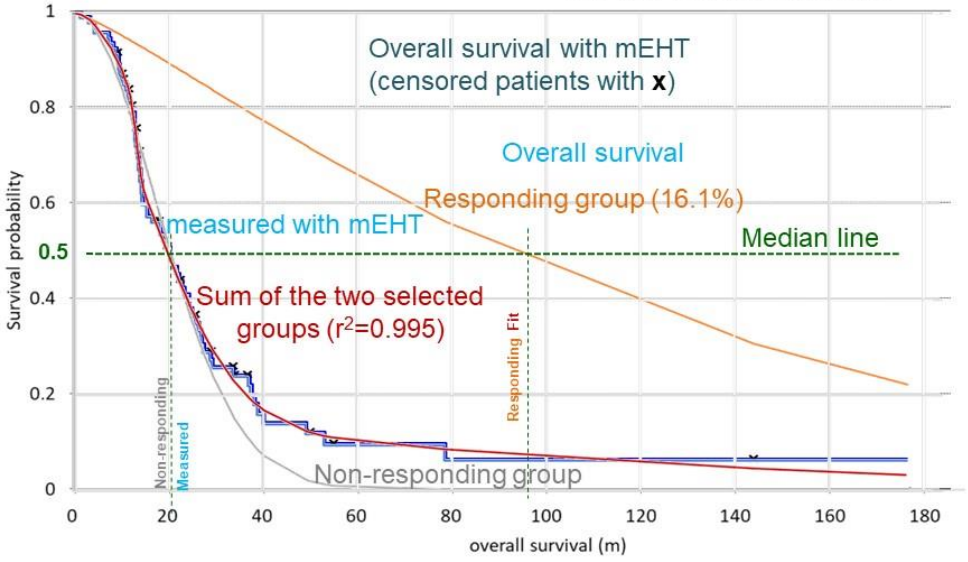


Study of advanced glioblastoma multiform, monotherapy

Sahinbas H, et al.(2007) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas. Deutsche Zeitschrift fuer Onkologie 39:154–160

Number of patients
- active arm n=94 (single institution)

Decomposition to responding and non-responding groups



Modified Hardin-Jones-Pauling (HJP) method

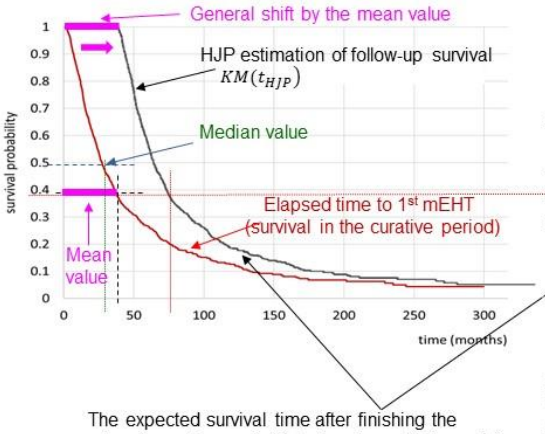
HJP argument: the expected survival of the patients in a follow-up time of a study is the average time involved in the study added to the final time of the observation.

Our assumption: the expected survival in palliative period can be calculated from its elapsed time

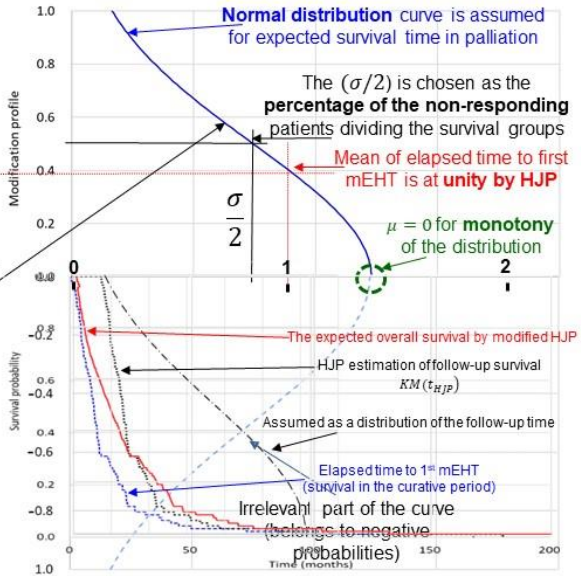
Challenge: Patient who had entered in palliative phase early has less probability to survive longer.

Modified HJP estimation

$$KMm(t_{HJP}) = \frac{KM(t_{HJP})}{\alpha\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(KM(t_e)-\mu)^2}{2\sigma^2}\right)$$

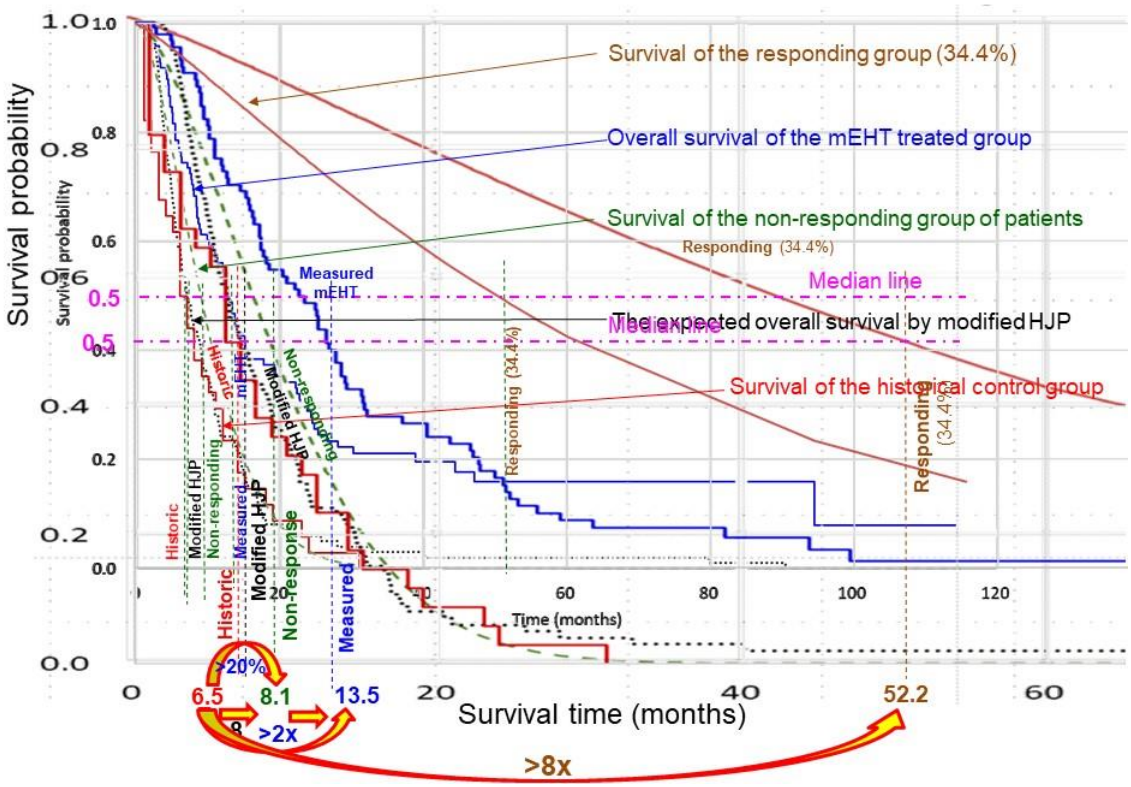


The expected survival time after finishing the conventional curative period (starting the palliative only) is the convolution of the HSP estimation and the normal distribution fit to the KM curve.



Pauling L, Herman ZS; (1989) Criteria for the validity of clinical trials of treatments of cohorts of cancer patients based on the Hardin Jones principle. Proc. Natl. Acad. Sci. USA, 86:6835-6837

Verification of modified HJP estimation



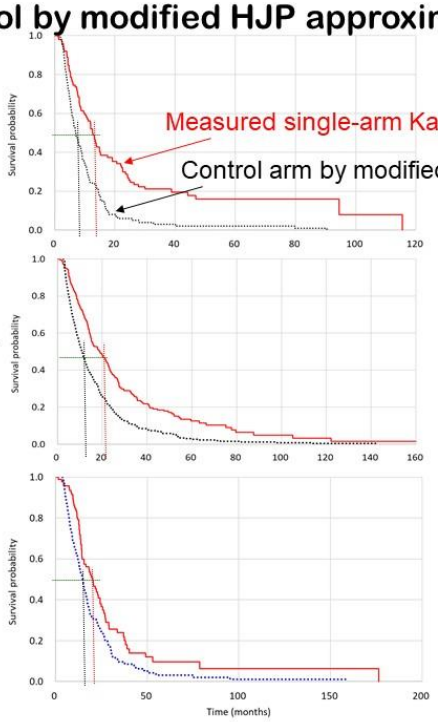
Quasi-control by modified HJP approximation

Overall survival

pancreas carcinoma

non-small-cell lung cancer

Glioblastoma multiform



The job is done

- ☑ The problem of the evidences in advanced diseases
- ☑ The general behaviour of the survival curves
- ☑ The strategies of studies
- ☑ Evaluation examples: pancreas, lung, glioblastoma

Thank you very much for your attention

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PROGRAM FINANCED FROM THE NRDI FUND

How to set up an individual program of hyperthermia and conventional treatment in heavily pretreated cancer patients

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Presented at the 37th ICHS, Thessaloniki

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www.oncotherm.com/sites/oncotherm/files/2019-10/How_to_set_up_an_individual_program.pdf

Hyperthermia is not sufficient as sole treatment. Even though there are experimental studies on cancer cells and in animals showing that hyperthermia may kill cancer cells, in patients up to now the results are not satisfactory.

But hyperthermia may serve as an important tool to improve the efficacy of conventional treatments like chemotherapy or radiation. This has been shown in numerous studies in particular in advanced, recurrent or metastatic disease. But to achieve good results it is not enough to just perform hyperthermia. A skilful setting of hyperthermia and conventional treatments is crucial.

There are not only different types of hyperthermia (superficial, deep-regional, whole-body hyperthermia), there are also several different drugs of chemotherapy and different techniques of radiation which must be put together in a correct order to achieve best possible success.

For first- or second-line treatment of cancer there are in general guidelines clearly showing possible success rates of certain treatments whereas in heavily pre-treated patients there are no guidelines anymore. So individual treatment concepts have to be set up.
In three exemplary patients (pancreatic cancer with peritoneal carcinosis, recurrent synovial sarcoma and non-small-cell lung cancer) treatment strategies are explained and the outcome discussed.

Patient 1: Diagnosis: Pancreatic cancer with peritoneal metastases

Oncological history:

11/15	Advanced cancer of pancreatic tail. Distal pancreatectomy, splenectomy, left colectomy.
01/16	FOLFIRINOX 12 cycles.
03/17	Carcinosis of gall bladder. Cholecystectomy. Pembrolizumab for 10 cycles. Progressive peritoneal carcinosis.
10/17	T-cell immunotherapy, PD.
12/17	Ileus and jaundice. Removal of parts of small intestine removed. Ileostomy. Bile duct metal stent
02/18	Subileus, nasogastric tube, parenteral nutrition (Image 1)

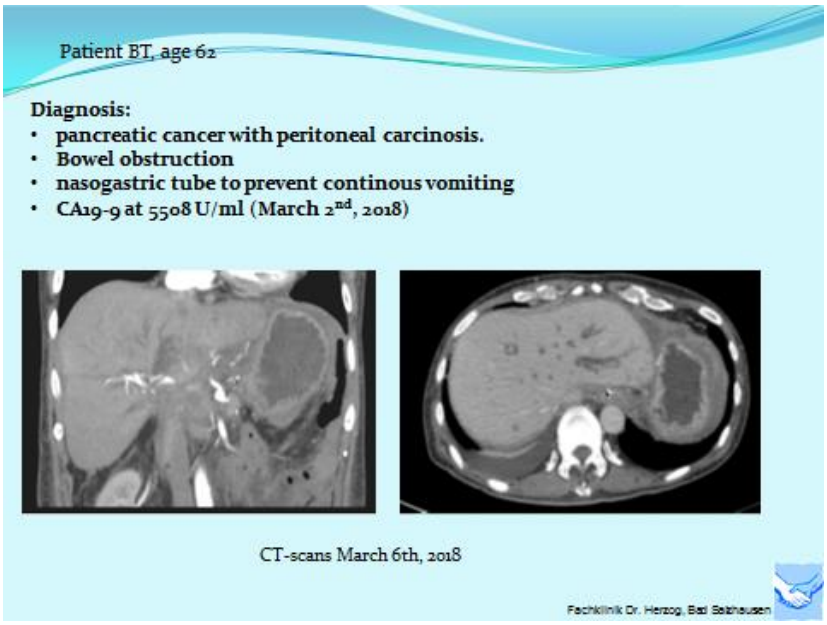

Image 1

Problem: The patient was heavily pre-treated with chemotherapy (Folfirinox), immuno-therapies and several surgeries. He came to us in a terminal situation, was not able to eat anymore and had a nasogastric tube because of continuous vomiting. The tumor marker CA19-9 was >5.000. The patient was extremely weak and in pain. No treatment options and no likelihood of response to chemotherapy anymore. (Johns Hopkins center, USA) To decide about a treatment in such a difficult situation it is necessary to consider all relevant factors. (Image 3)

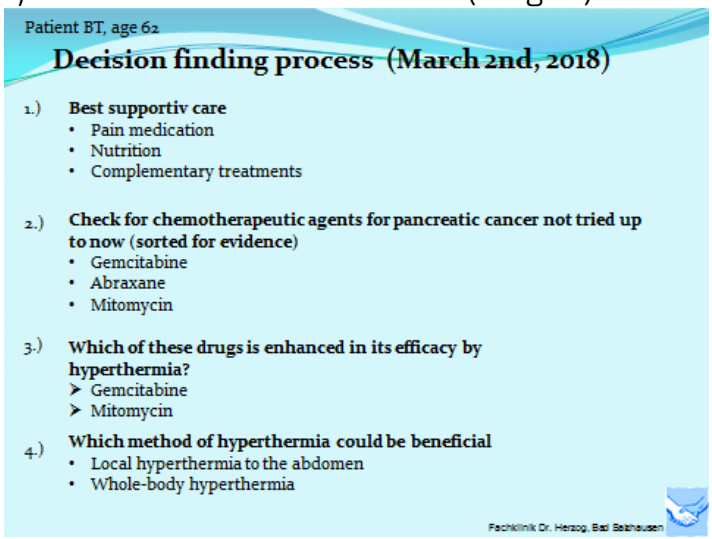

Image 2

Solution:

03/18 Local and whole body hyperthermia (Oncotherm EHY 2000, Iratherm 2000) In combination with Gemcitabine. Parenteral nutrition and complementary treatments.

Result: Decrease of tumor markers. Normal food uptake and bowl function, good quality of life again.

10/18 Maintenance therapy with Capecitabine and hyperthermia.

04/19 Cholangitis and stenosis of bile duct stent. Placement of 2 plastic stents into the metal stent. Continuation of Capecitabine and hyperthermia.

06/19 Lasting PR, Ca19-9 at 73,6ng/ml, good quality of life.

Comment: Given the situation of this patient in the beginning a survival beyond a few weeks was not likely. Now 1 1/2 years after first admission the patient is still alive and in a good condition. Only the combined treatment adding hyperthermia to chemotherapy can explain this outcome. After Gemcitabine alone in his condition such a result never would have been expected. (Image 3)

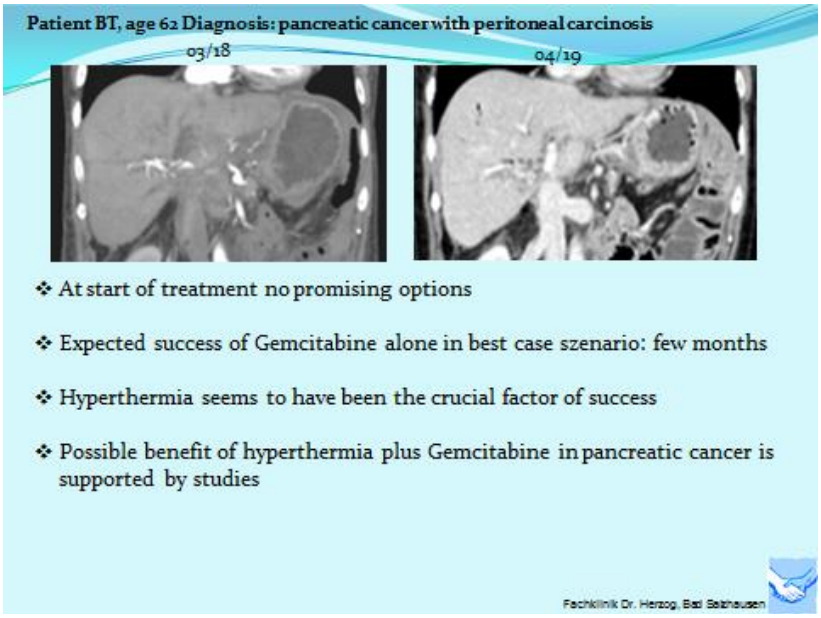

Image 3

Patient 2: Diagnosis: Synovial sarcoma of left knee

Oncological history:

01/16	Lump at left knee, at biopsy synovial sarcoma
03/16	Resection, stage pT2R0
04/16	Radiation of the distal right femur
12/16	Local recurrence above the field of radiation
01/17	Resection of recurrence, Radiatio and brachytherapy
06/17	Grossly swollen left leg, thrombosis of the vena femoralis caused by large tumour metastases in the left groin.
08/17	Chemo-immunotherapy with Doxorubicin and Olaratumab, PD
10/17	Carboplatin and Gemcitabine, PD
12/17	Pazopanib, PD
02/18	One cycle of Ifosfamide high dose, not tolerated (encepalopathy). Progression of the disease resulting in a tumour of more than 11 cm diameter in the left groin reaching into the pelvis, compressing bladder and ureter and growing around the blood vessels and nerves of the left leg. 3 more large masses along and around the arteria femoralis down the left thigh, the lowest mass a few centimeters above the inner left knee. (Image 4)

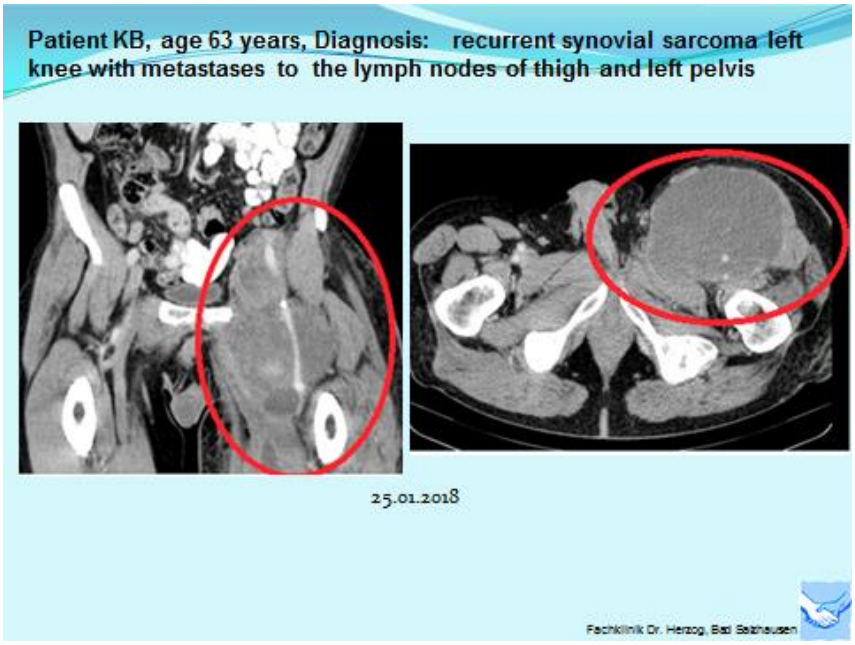

Image 4

Problem: Metastatic sarcoma of the left knee spreading into the lymphatic tissues along the left thigh up to the pelvis. Progression after 3 lines of chemotherapy and immunotherapy. The last chemotherapy with Ifosfamid in high dose he almost had not survived. No other treatment options now than left hemipelvectomy and amputation of the left leg. (Image 5)

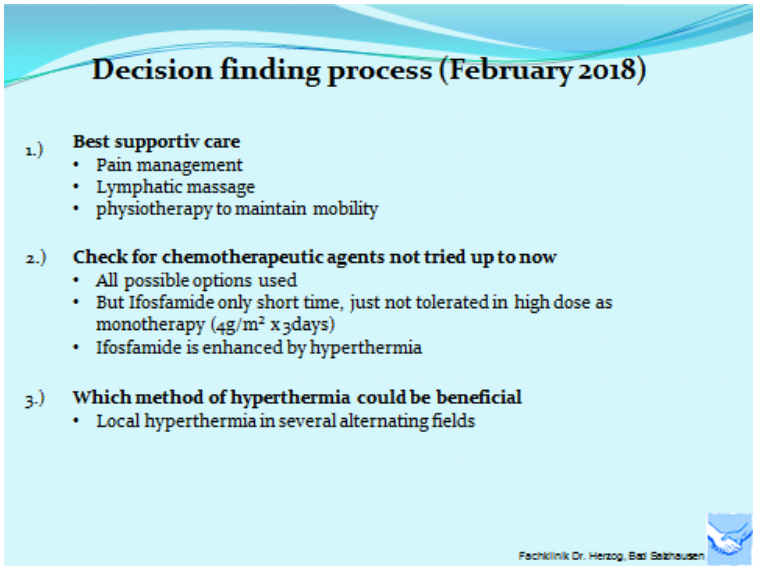

Image 5

Solution: Continuation of Ifosfamide but in lower doses (2,2 g/ m^2/ 24 hrs x 3 days) combined with local hyperthermia (Oncotherm EHY 2000) to the metastatic sites at pelvis and left thigh.

Result: Very good partial remission. The patient was free of pain, could walk again without crutches, the swelling of the leg had come down. (Image 6)

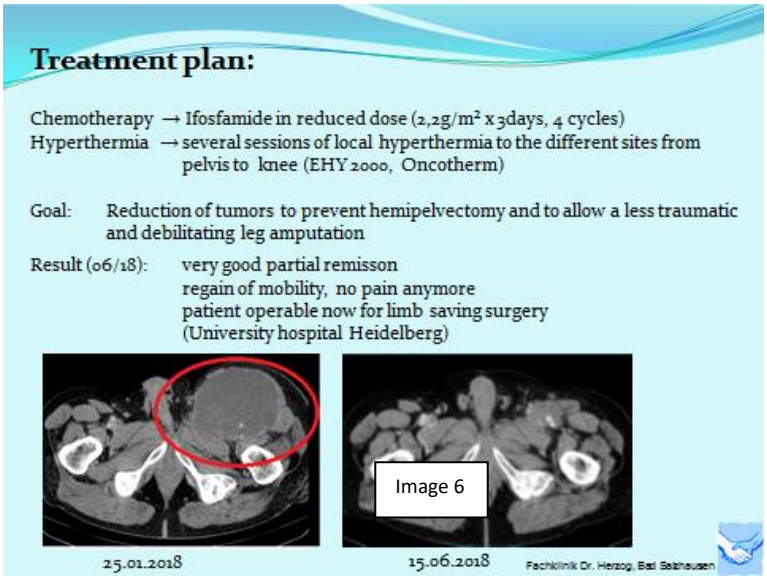

Image 6

Comment: Because of the good response amputation was not necessary anymore. Limb saving treatment was now considered. This result can only be explained by the additional treatment with hyperthermia.
But the patient didn't want to have surgery because od possible damage. (Image 7)

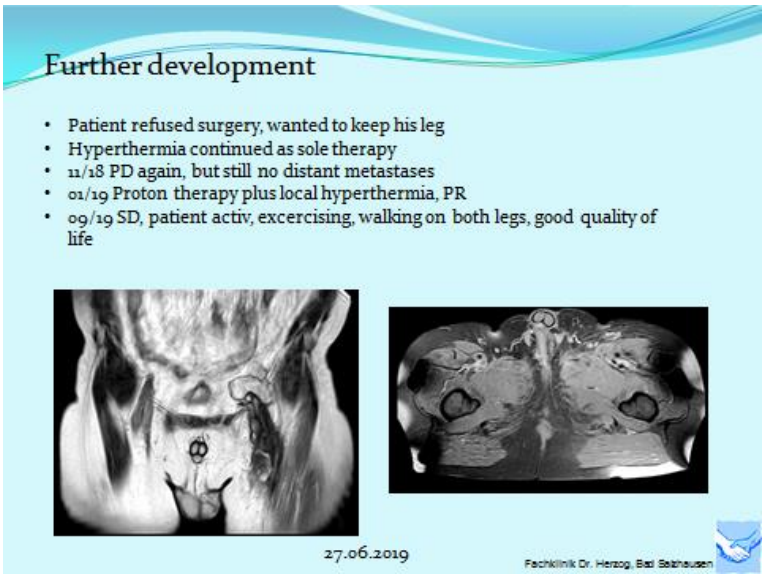

Image 7

Patient 3: Diagnosis: NSCL (adenocarcinoma) with metastases to the brain (EGFR pos.)
Oncological history:

01/11 Adenocarcinoma of the left lung with brain metastases (T3, M1), surgery of the brain metastases, chemotherapy with Carboplatin and Vinorelbine, radiation of the lung tumour and the brain.
07/11 Progression of the brain metastases, treatment with Gammaknife.
10/11 Progression in the lung, Pemetrexed
02/12 Progression in the brain and the lung, treatment with Gammaknife for the brain. Treatment with Tarceva for the lungs, progressive disease. (Image 8)

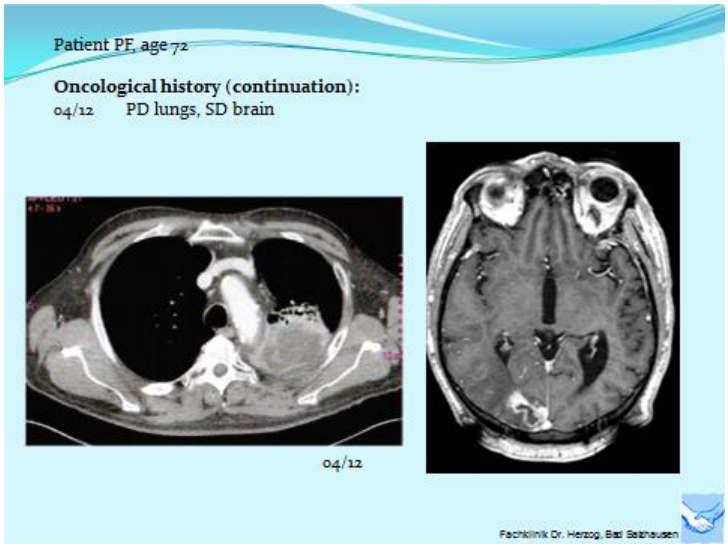

Image 8

Problem: Progressive disease after multiple chemotherapies and targeted therapy. He suffered from caugh and chest pain. No treatment options anymore, the tumor was considered as resistant to further chemotherapy. (Image 9)

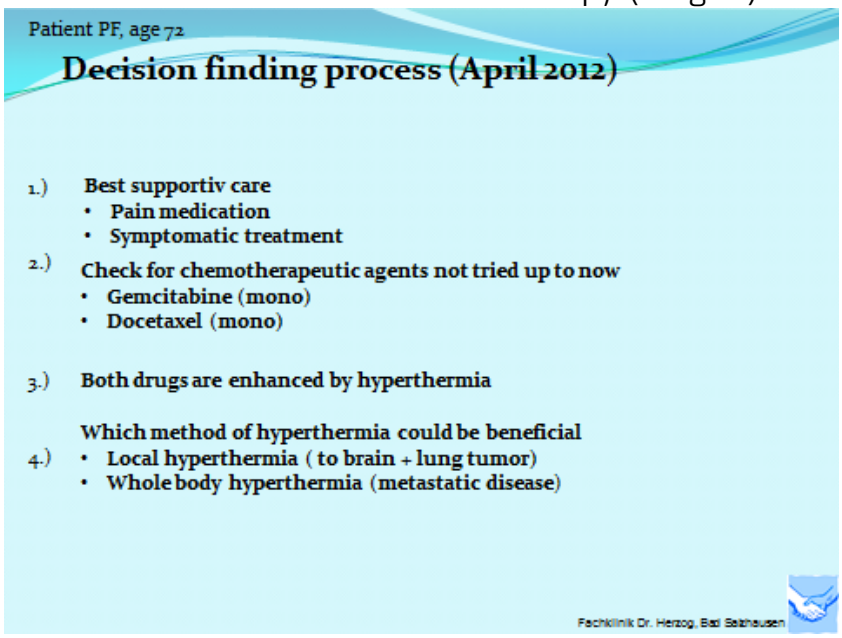

Image 9

Solution: Whole body and local hyperthermia in combination with Taxotere in moderate doses.

Result: Partial remission of the pulmonary disease, no new activity in the brain

Further development:

03/15 Stereotactic radiation of the remaining lung tumor

Since 10/15 normalization of tumor markers, no evidence of active disease. (Image 10)

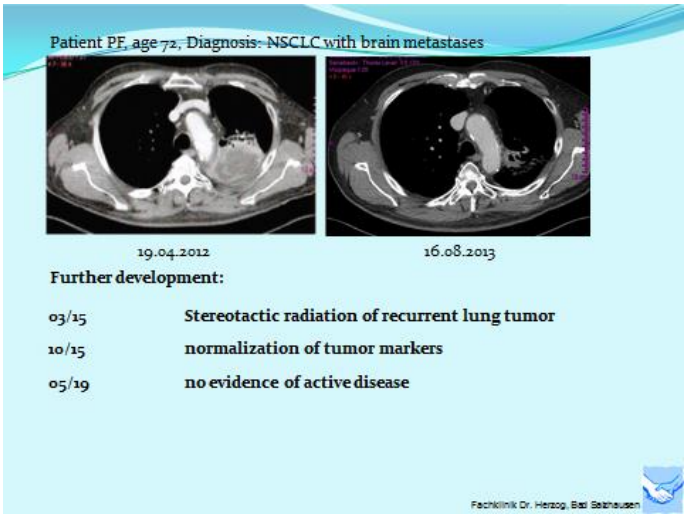

Image10

Comment: In this patient the likelihood of response to further chemotherapy was little and if at all only for a short time. Hyperthermia in this case very likely helped to overcome resistance and enabled long term survival. The patient has now been free of disease for more than 4 years (since March 2015), he is in a good quality of life. He comes every 6 months for check-up.

Conclusion

Even in heavily pre-treated patients there is a chance to achieve a good and long-lasting treatment success. Hyperthermia in these cases seems to be the crucial tool. The setting in each situation has to be a specific combination with adapted programs of conventional treatments like chemotherapy and radiation.

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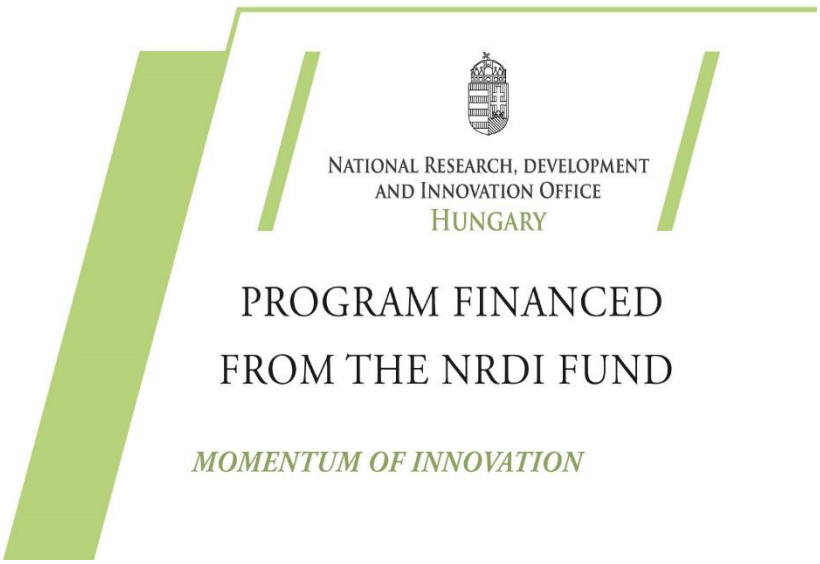
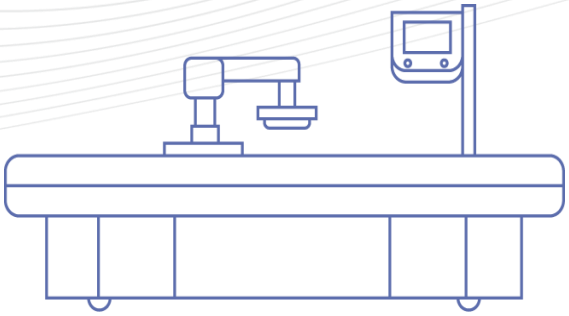


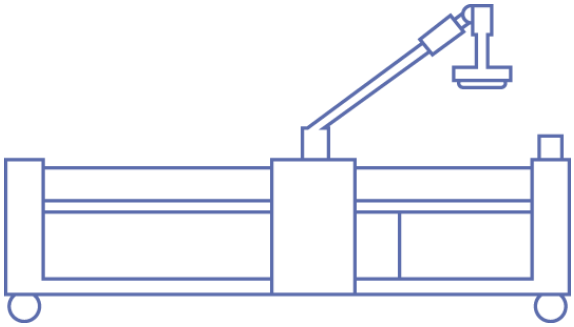
THE ONCOTHERMIA METHOD & DEVICES

- Oncothermia is based on the classical method of Hyperthermia, one of the oldest cancer treatment methods. Unlike conventional Hyperthermia, Oncothermia does more than simply warm up deep layers of tissue. It combines such warming with a modulated electric field, with a carrier frequency of 13.56 MHz, which is generated by two active electrodes.

EHY-2030

The EHY-2030 is our latest development in the treatment of loco-regional (including deep and surface) tumors. The newly designed device includes the Smart Electrode Seystem (*SES*), the plug-in Patient Management System (*PMS-100*) and a user-friendly touch screen display with full system control. The new RF generator with increased power has been developed with a new intelligently controlled step motor tuning system for rapid impedance matching to achieve faster tuning times.



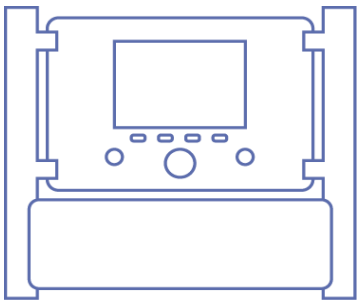


EHY-2000$_{plus}$

The EHY-2000$_{plus}$ is a widely accepted system for loco-regional deep mEHT applications. This model has been used for treatment worldwide for more than 20 years. Popular, versatile device, applicable for a range of solid tumors and improved over the years through feedback from our doctors and experts and the requirements of patients and the people treating them. The EHY-2000$_{plus}$ is an easy to use and highly reliable device.

EHY-1020

The EHY-1020 is specifically designed to treat prostate diseases. Both malignant and benign tumors (BPH) can be treated using this system. It uses a catheter with built-in electronics and counter electrode. The EHY-1020 system is compact and easy to use. The method has been successfully used by our customers since 2010 with high success rates and minimal side effect.



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