

A publication of Oncotherm

December 2016

Volume 18.

ISSN 2191-6438

ONCOTHERMIA JOURNAL

The 34th Annual Conference of the International Clinical Hyperthermia Society (ICHS)

Report from ICHS Pesaro

Quo vadis oncological Hyperthermia Update 2016

Combining hyperthermia with other anticancer methods

Workshop Local Hyperthermia

The place and role of clinical hyperthermia in oncological thermotherapy: let's define what we are talking about

Pharmacoeconomic study of oncothermia (modulated electro-hyperthermia) in the treatment of lung cancer

Hyperthermia combined with radiation in cervical cancer

Comment to C.A. Minnaar's results

Pakistan has highest breast cancer rate among Asian countries

Bestmögliche Ergebnisse der Oncothermie (Elektrohyperthermie) bei der Therapie von Karzinomen und Sarkomen in Kombination

The Immune Regulating Effect of Hyperthermia in Combination with TCM on Cancer Patients

Oncothermia New Method of Tumor Therapy

Case reports from Oncothermia Clinic, Karachi, Pakistan. Early experiences

Editorial



Dear Readers,

this year a very important conference took place in Italy: The 34th Annual Conference of the International Clinical Hyperthermia Society (ICHHS) which was held in Pesaro on September 22nd. Prof. Giammaria Fiorentini was the host of this wellorganized event and about 100 participants came together to discuss experiences and new insights of hyperthermia.

Doctors from all over the world came together and represented the worldwide use of hyperthermia. The most important results and approaches are presented in this journal. We also provide you with a summary of the meeting and some information about what is planned for the future of hyperthermia.

This will give you a good idea of what Dr. Brenner called "[...] a perfect meeting in Italian style, with high scientific presentation and level of debate, awards for scientists and patients. A perfect mix that relaunch our society."

Apart from the conference publications, this issue of the Oncothermia Journal also contains a detailed report about Oncothermia: background, approaches and perspectives.

Enjoy reading and contact us any time in case you have any questions or remarks.

Sincerely yours,

Prof. Dr. Andras Szasz

Liebe Leserinnen, liebe Leser,

am 22. September diesen Jahres fand in Pesaro, Italien, eine sehr bedeutende Konferenz statt: „die 34te Konferenz der internationalen klinischen Hyperthermie Gesellschaft (ICHHS)“. Prof. Giammaria Fiorentini war der Gastgeber der gut organisierten Veranstaltung auf der über 100 Teilnehmer zusammen kamen, um sich über Erfahrungen und über neue Erkenntnisse bezüglich der Hyperthermie auszutauschen.

Ärzte aus der ganzen Welt kamen zusammen und repräsentierten den weltweiten Gebrauch der Hyperthermie. Die wichtigsten Ansätze und Ergebnisse stellen wir in diesem Journal dar. Außerdem geben wir Ihnen eine Zusammenfassung der Konferenz, sowie eine Übersicht über das, was in Bezug auf die Hyperthermie zukünftig geplant ist.

Dies ermöglicht Ihnen eine bessere Vorstellung davon, was Dr. Brenner ein „(...) perfektes Treffen in italienischem Stil“ nennt. Großartige wissenschaftliche Präsentationen und Diskussionen auf hohem Niveau, Auszeichnungen für Wissenschaftler und Patienten. Eine perfekte Mischung, die unsere Gesellschaft bereichert.

Neben den Publikationen der Konferenz beinhaltet dieses Oncotherm Journal außerdem einen ausführlichen Bericht über Oncothermie: Hintergrund, Ansätze und Perspektiven.

Wir wünschen Ihnen viel Vergnügen beim Lesen. Bei Fragen oder Anregungen können Sie uns gerne kontaktieren.

Mit freundlichen Grüßen,

Prof. Dr. Andras Szasz

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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 Oncothermia 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 Oncothermia 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 erleichtern, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope

The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to support them, making a collective for using the results and making it common for general use. The Oncothermia Journal has an open-minded character, expecting the 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 oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities, and treatment optimization.
- *Biological Studies:* Mechanisms of oncothermia, thermal-or non-temperature dependent effects, response on electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- *Techniques of oncothermia:* Technical development, new technical solutions, proposals.
- Hypotheses, suggestions, opinions to improve the oncothermia 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.Oncothermia-Journal.com.

1. Selbstverständnis und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia 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.

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All submissions should be made online at the Oncothermia Journal by email Oncothermia-Journal@oncotherm.org.

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Manuscripts must be written in English, but other languages can be accepted by special reasons, when it has an English abstract.

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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 identified, whose email address has to be provided with full contact details.
- *Abstracts.* Abstracts should include the: Purpose, Materials and Methods, Results, 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 reference to the text. Figure files will ideally be supplied as jpg-file (300dpi for photos).
- *References.* Oncothermia 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.
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- **Zitate.** Das Oncothermia 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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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.

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7. Werbung

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

8. Legal responsibility

Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any actual publications. The Editorial Board has the right to reject any publications if its validity is not enough controlled or the Board is not convinced by the Authors.

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

9. Reviewing

The Oncothermia Journal has a special peer-review process, represented by the Editorial Board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of Reviewer will not be signed, her/his name will be handled confidentially. Papers which are not connected to the scope of the Journal could be rejected without reviewing.

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Die Texte für das Oncothermia 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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Report from ICHS, Pesaro

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Report from ICHS, Pesaro

The 34th Annual Conference of the International Clinical Hyperthermia Society (ICHS) was held in Pesaro, Italy on September 22nd 2016. The meeting was very successful with more than 100 attending doctors and Prof. Giammaria Fiorentini was its chairman. The Conference was dedicated to the memory of Dr. Gianfranco Baronzio, a pioneer of hyperthermia, who suddenly deceased this year due to heart attack.

The conference offered the chance to meet experts of all fields of hyperthermia coming from several countries of the world, and to learn their experiences and researches in order to explore hyperthermia treatment application in cancer and other diseases.

An important part of the conference was dedicated to the presentation of results about the efficacy of capacitive hyperthermia alone or in combination with chemotherapy and radiotherapy.

The conference was divided into seven sessions devoted to many aspects of hyperthermia. The theme of the congress was the development, over the past 20 years, of modern hyperthermia technology that advanced rapidly in the clinical treatment of various benign and malignant diseases.

Hyperthermia is now widely used in a lot of countries. Its curative and palliative treatment effects in combination with other treatment methods are extensively reported. Today the doctors can find in the “tools box” to treat tumors with hyperthermia as a significant part of entire cure.

The first session of the congress was dedicated to “Biologica basics, experimental and technical studies on Hyperthermia”. Dr. Von Ardenne from Germany reported the technique of whole body hyperthermia and clinical records of treatments done for fibromyalgia syndrome. Dr. Di Dia from University of Turin presented the critical issues in the use of double antennas in superficial hyperthermia therapy.

Professor C. Pang reported interesting data on hyperthermia and oncothermia as an important part of natural medicine. His presentation entitled “Place and role of clinical hyperthermia in combination with traditional Chinese medicine” was very significant and showed that together with official medicine the integrative natural therapies also play very important role in actual treatments as in the medical history of human development. With the development of modern medicine and the progress of the society, it has been well perceived that natural therapies, due to their safety and less side-effect, have attracted more attention. Natural therapies, including traditional Chinese medicine, are gradually becoming a new model of the modern medical treatment in the world.

Dr. Sergey Roussakow from Moscow presented the place and role of clinical hyperthermia in the system of thermotherapy in oncology. He stressed that let's define what we are doing in this field.

K. W. Sung, N. Winters and T. Morita K.W. were the discussants of this session.

In the second session, the topic was “Clinical evidences of increasing survival adopting hyperthermia alone or in combination with anti-cancer methods”.

Dr. Brenner from Tel Aviv reported personal experiences on a lot of clinical records and many international studies where hyperthermia is a landmark stone in the tools box of cure. He reported the possible combinations with biologicals and new drugs.

Dr. Hussein from Germany presented the results of combination of traditional chemotherapy and hyperthermia in colorectal cancer patients showing the increasing results of this double approach.

Dr. Ranieri from the National Cancer Institute of Bari, South Italy presented very interesting new studies reporting how to increase tumor antigens using hyperthermia before anti PD-1 therapy. His experience showed how to move from theory to practice. It seemed that oncothermia and extreme hyperthermia, as microwave ablation or RFA, could enhance the immune responses to pembrolizumab and nivolumab. Dr. Ranieri won the award of ICHS 34th edition with this work.

Then Dr. Roussakow reported the pharma-economic studies of oncothermia for the treatment of lung cancer showing many advantages in respect to chemotherapy in III and IV cancer stages.

Prof. Andras Szasz presented a lecture entitled: “Quo vadis oncological hyperthermia: update 2016”. He underlined all the main topics of the field reporting highlights, significant data and studies, and was awarded for his role in oncothermia development as leader of oncothermia field.

Dr. Z. Hongyu was the discussant of this session.

The third session was devoted to results and perspective of hyperthermia associated with radiotherapy and chemotherapy. Dr. Minnaar Straus from South Africa reported a precious experience in the treatment of cervical cancer in a country with high incidence of poverty and with many HIV positive patients.

Prof. Maluta from Padua, Italy presented a worldwide status of hyperthermia.

Dr. Di Dia reported the results of combination of hyperthermia and radiotherapy in pancreatic cancer. Dr. Dall'Oglio from University of Verona presented the favorable integration between radiotherapy and hyperthermia in prostatic cancer.

Dr. Z. Xinting and T. Khuayjarernpanisk were the discussants of this section.

The fourth session started after the lunch break with the workshop on local hyperthermia done by Dr. Oliver Szasz. He presented an overwhelming lecture with many actual hypothesis and studies. After Dr. Szasz' s overture Dr. Hussein presented the second workshop on whole body hyperthermia.

The fifth session was devoted to extreme hyperthermia in lung and liver lesions done by mean of RFA and microwave ablation. Dr. Di Ceglia, from the National Cancer Institute of Bari, South Italy presented patients treated with RFA in the lungs and Dr. Tarantino from Naples reported wide experiences of micro wave ablation in liver metastases. He presented this paper very successfully also in Barcelona where a month ago the European Congress of Interventional Radiology (CIRSE) was held.

The sixth session was dedicated to peritoneal surface malignancies treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (part I). Dr. Kusamura from Japan reported the state of the art, then Dr. De Simone from the National Cancer institute of Turin, Italy and Dr. Sammartino from Catholic University of Rome showed interesting data of this approach in ovarian cancer. They said that in selected patients after adequate cytoreductive

surgery the hyperthermic peritoneal perfusion could have better results than surgery alone. Then Dr. Graziano from Oncology Unit Azienda Ospedaliera Marche Nord Pesaro, Italy reported the use of C-Parp inhibitors in ovarian cancer.

Dr. Deraco from the National Cancer Institute of Milan discussed in the debate the opportunity to combine peritoneal perfusion with external hyperthermia and oncothermia. Further studies should be warranted on this interesting topic.

The seventh session was devoted to peritoneal surface malignancies treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (part II).

Dr. Deraco from the National Cancer Institute of Milan reported a very high scientific presentation on peritoneal mesothelioma showing the superiority of surgery combined with chemotherapy administered by hyperthermic perfusion in term of responses and survival. Dr. De Manzoni from the University of Verona reported their experiences on gastric cancer and Dr. Catalano from Oncology Unit Azienda Ospedaliera Marche Nord Pesaro, Italy presented an interesting talk on ramucirumab, a new drug against gastric cancer.

Dr. Baratti from the National Cancer Institute of Milan made a final lecture on peritoneal carcinosis from colorectal cancer.

In the final statements and conclusions Prof. Pang, Prof. Fiorentini and Prof. Szasz underlined the needs to have more well prepared studies and clinical trials to reinforce hyperthermia's positions in the scenario of oncological treatment options.

They said: "Up to now every one of us reports a lot of personal experiences, small series of patients treated differently and successfully. In the literature, there are few new believable data and trials compared with the high possible theoretical and clinical advantages offered by hyperthermia, so we must promote well planned and conducted trials, better if some of those randomized. We should organize, in our ICHS, a steering committee able to write some simple, easy to do, repeatable, feasible studies."

They stressed that another problem is the poor economic resources for hyperthermia. The investments of industries producing the hyperthermia devices and machineries are very low compared to those spent by pharmaceutical corporations. So, we need to find a way to join with their programs in order to receive economical support for common studies. We have a great opportunity now. With the new generation of immune-stimulating drugs, such as ipilimumab, nivolumab and pembrolizumab we have an extraordinary and amazing opportunity to combine these with hyperthermia.

Our immune system, even if stimulated by these new drugs, can recognize only 5% of all cancer antigens. So, the results are still poor in the fight against cancer, even if the total costs have increased to thousand billion of dollars.

The vast majority of researchers engaged in the field of immunology are thinking that loco-regional approach as Radiofrequency ablation, intra-arterial application of drugs, modern radiotherapy and hyperthermia, above all in my opinion, can induce more amounts of neo antigens.

Hyperthermia, in particular oncothermia, will produce not only neo antigens damaging the membrane of tumor cells, but also increasing the lymphocyte trafficking inside the tumor, amplifying the chances to recognize antigens and inducing a positive and favorable immune response.

After hyperthermia, an increasing amount of antigens will be freed and recognized and so more response should be obtained with these new immune-drugs, thus reducing costs and toxicity.

The Professors concluded that “ICHS is a worldwide scientific Society that need to be supported by us all. Together we do it better and better.”

At the final speech of the Conference Prof. Pang invited all the doctors and scientists to take part in the next 35th annual Conference of the International Clinical Hyperthermia Society (ICHS) that will be held in China in November 2017.

In the central part of the congress, other awards were given to Dr. Carrie Minaar Strauss, Dr. Sergey Roussakow and Prof. Clifford Pang for their scientific contribution and Dr. Brenner received a special prize from Oncotherm as best research of the congress.

Two men (35 and 29 years old) were also awarded for their courage and wish to live after 12 and 4 years from the treatment of their anaplastic astrocytoma with hyperthermia. A filmmaker made 2 moving videoclips dedicated to their lives which deeply touched the audience.

The congress was highly appreciated and as Dr. Brenner said: “It is a perfect meeting in Italian style, with high scientific presentation and level of debate, awards for scientists and patients. A perfect mix that relaunch our society.”

Quo vadis oncological Hyperthermia Update 2016

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34th Annual Conference of the
International Clinical Hyperthermia Society (ICHS)
22 September, 2016; Pesaro, Italy

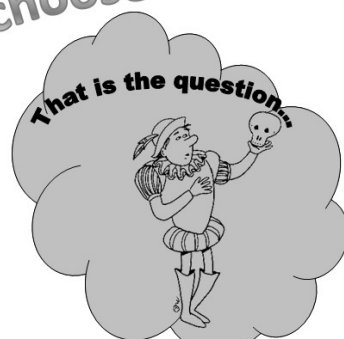


Quo vadis oncological Hyperthermia Update 2016

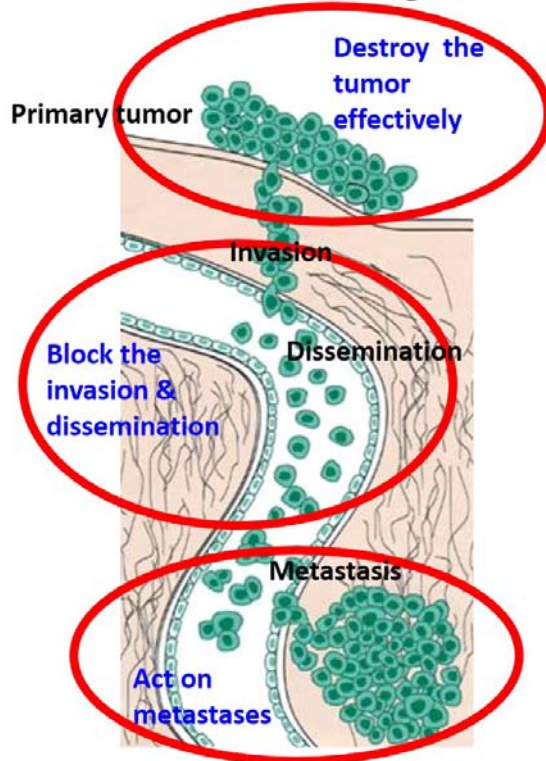
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Head of Biotechnics Department of St. Istvan University, Hungary
Visiting professor (bio-electrodynamics) at Pazmany P. Catholic University, Hungary
Visiting Professor (fractal physiology) at Chiba University, Japan

To treat or not to treat?
To heat or not to heat?
To choose or not to choose?



Challenge of targeting in oncology



Malignancy looks local, but it isn't.

Which option do we have in refractory cases when the standard protocols fail?



Which treatment could be applied, which one is not toxic and effective?

Challenge of impact of cytotoxic chemotherapy on 5-year survival in 2004 (American adults)

Malignancy	ICD-9	Number of cancers in people aged > 20 years*	Absolute number of 5-year survivors due to chemotherapy†	Percentage 5-year survivors due to chemotherapy‡
Head and neck	140–149, 160, 161	5139	97	1.9
Oesophagus	150	1521	82	4.9
Stomach	151	3001	20	0.7
Colon	153	13 936	146	1.0
Rectum	154	5533	189	3.4
Pancreas	157	3567	—	—
Lung	162	20 741	410	2.0
Soft tissue sarcoma	171	858	—	—
Melanoma	172	8646	—	—
Breast	174	31 133	446	1.4
Uterus	179–182	4611	—	—
Cervix	180	1825	219	12
Ovary	183	3032	269	8.9
Prostate	185	23 242	—	—
Testis	186	989	373	37.7
Bladder	188	6667	—	—
Kidney	189	3722	—	—
Brain	191	1824	68	3.7
Unknown primary site	195–199	6200	—	—
Non-Hodgkin's lymphoma	200 + 202	6217	653	10.5
Hodgkin's disease	201	846	341	40.3
Multiple myeloma	203	1721	—	—
Total		154 971	3306	2.1%

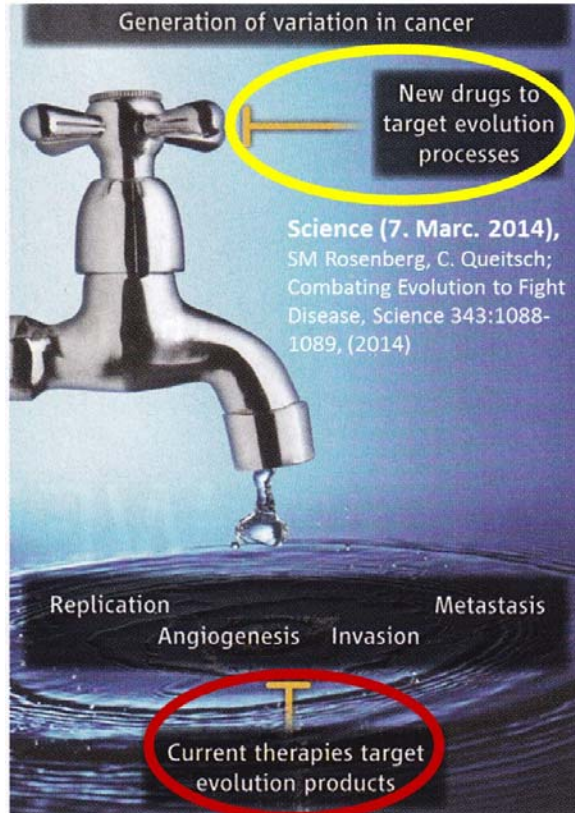
*Numbers from Ref. [22].

†Absolute numbers (see text).

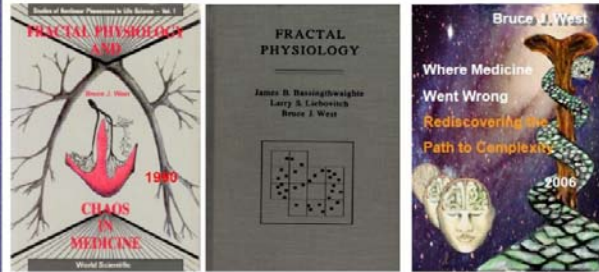
‡% for individual malignancy.

Morgan G, Ward R, Barton M (2004) The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin Oncol (R Coll Radiol) 16(8):549-560

Challenges with medical paradigm



Missing complexity
(where medicine went wrong)?

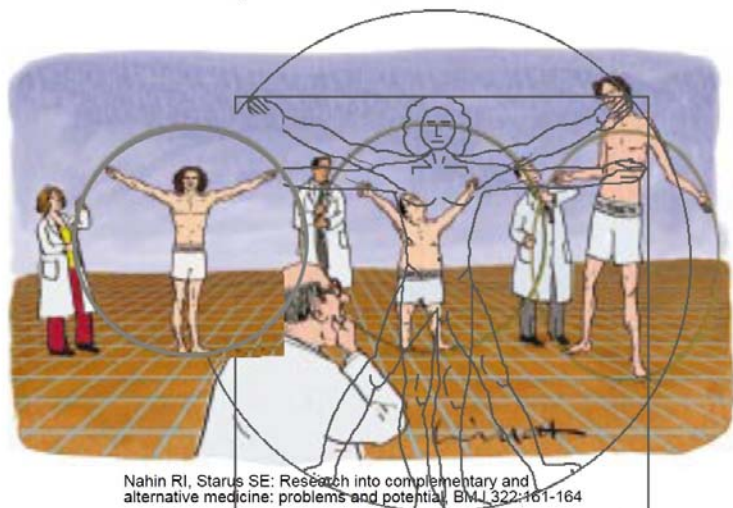


Cancer is loss of complexity!

New paradigm is
mandatory in
oncology!

Challenge of personalization

The necessary object of the treatment is
not the tumor itself, but the **PATIENT** with tumor!



When a study is well personalized, then
no perfect cohorts could be collected.

How to make cohorts? Poison everybody up to his/her tolerance limit.

Search for new medical possibilities

Present answers on challenges

➤ In radiotherapy:

- tomo-therapy,
- proton-therapy

➤ In chemotherapy:

- nano-applications,
- personalized therapies,
- targeted therapies
- cancer-stem-cell therapies,
- immune therapies
- check-point inhibitors

➤ In hyperthermia:

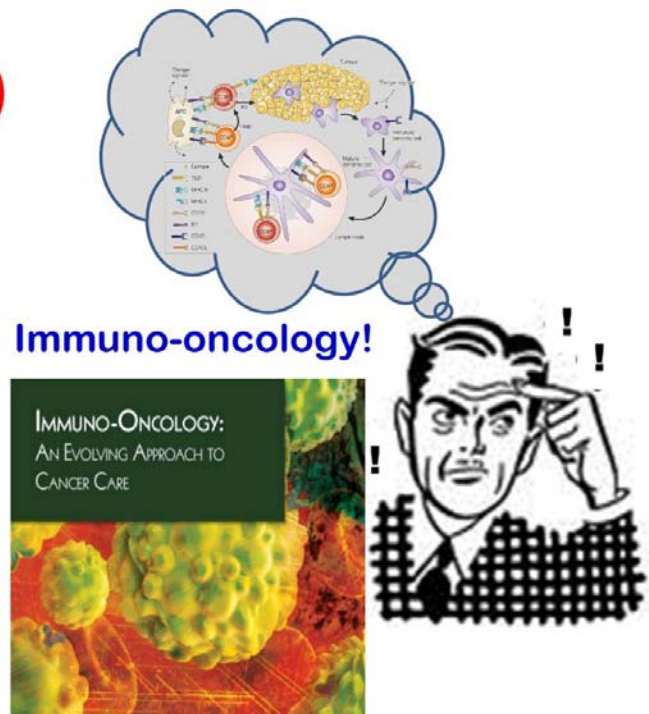
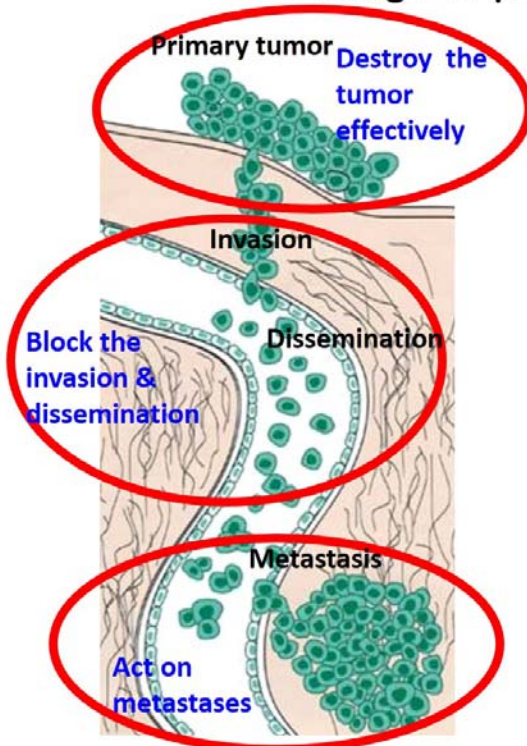
- interventional (invasive) hyperthermia (RF-ablation, laser induced hyperthermia, electroporation)
- nanoparticle-heating,
- immune-modulation by heat
- find new complementary applications

**Radio and chemo treatment modalities
are developing quicker than hyperthermia**

The change of paradigm is missing. How to think differently?

1. Think about the patient in his/her personal complexity
2. Be less toxic, do the treatment rather smartly and less aggressively
3. Use the personal immune activity of the patient
4. Think about the survival and quality of life instead of the response rates

Change of paradigm in oncology



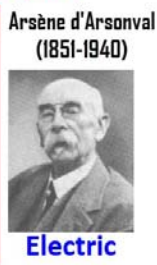
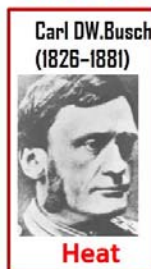
Hyperthermia is a good partner for change of paradigm!

To treat or not to treat?
 To heat or not to heat?
 To choose or not to choose?



Historic approach in oncologic hyperthermia

Local therapies

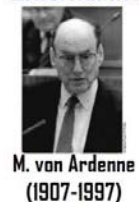


Whole-body therapies

Internal inducing

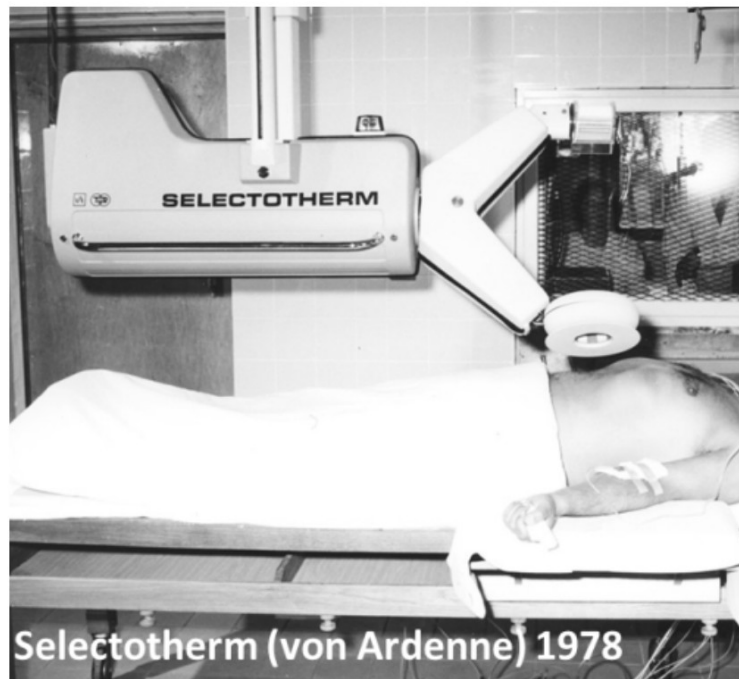


External inducing



Pioneering of the combined hyperthermia

M. von Ardenne
(1907-1997)



Selectotherm (von Ardenne) 1978

Modern approach in oncologic hyperthermia

Typical nowadays whole-body hyperthermia devices

Reflective
[Heckel Medizintechnik, Germany]



Filtered
[vonArdenne, Germany]



Extracorporeal (perfusion)
[Rand, Italy]



RF-capacitive
[Oncotherm, Germany]



Typical ablation hyperthermia device



Ablative [RF-3000, Boston Scientific, USA]

Typical nowadays local hyperthermia devices



Magnetic (inductive)
[Magforce, Germany]



Radiative (antenna array)
[BSD Medical, (Pyrexar) USA]

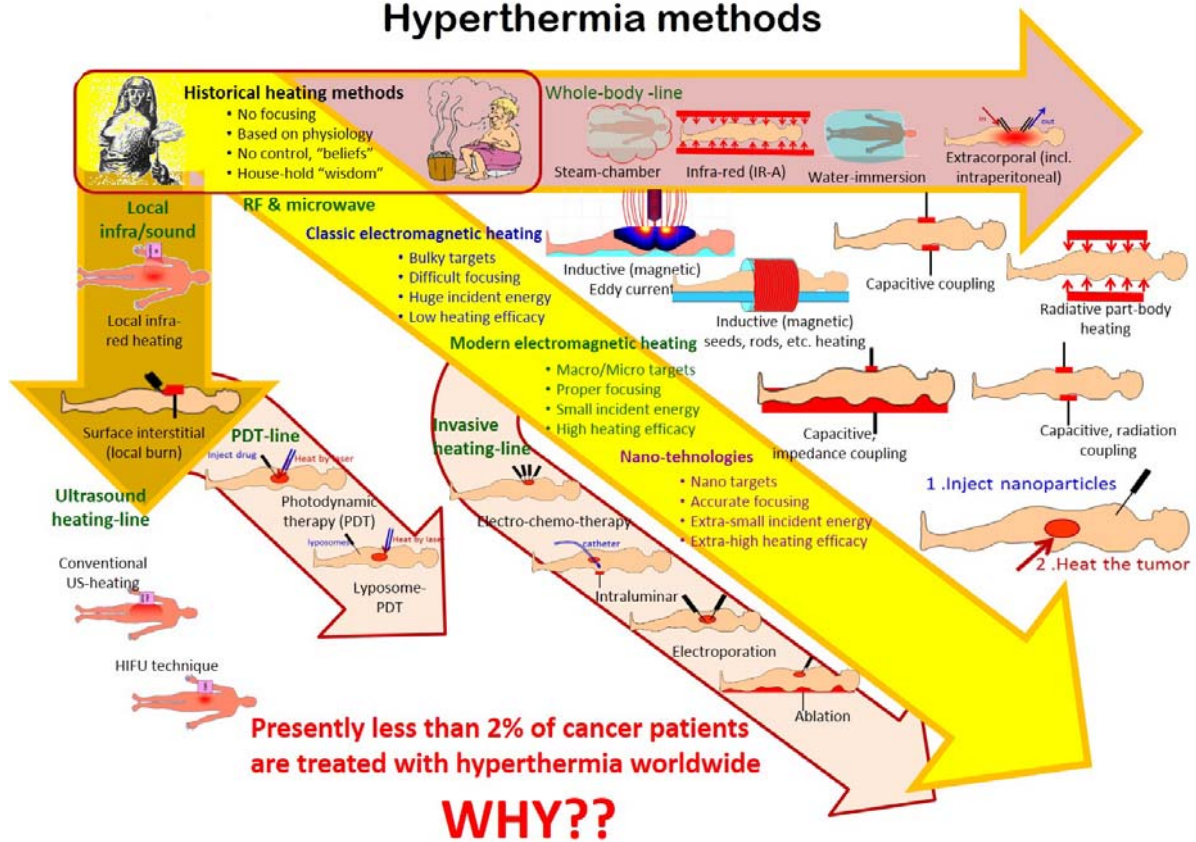


Electric (radiative capacitive)
[Celsius42, TCS, Germany]



Electric (radiative capacitive)
[Thermotron RF-8, Japan]

Hyperthermia methods



Challenges of the market

The conventional hyperthermia methods had lost their "attractive behavior", and they are abandoned in many University places.

No governmental University makes hyperthermia with Thermotron in Japan.

BSD closed its reference clinic at Duke University, USA.



Challenges of the market

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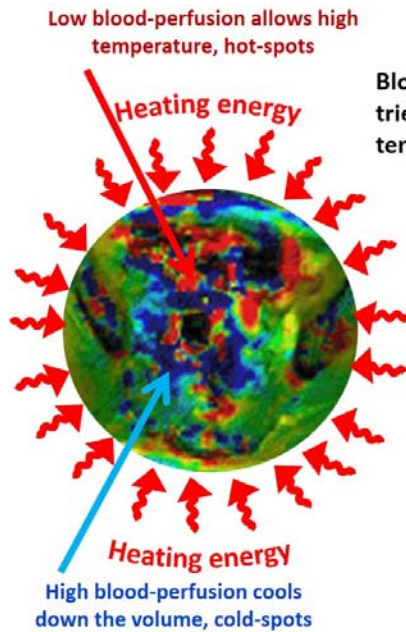
Controversies in clinical results. **WHY is it so?**



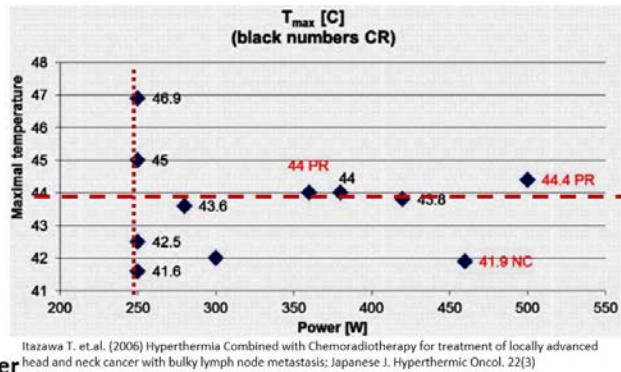
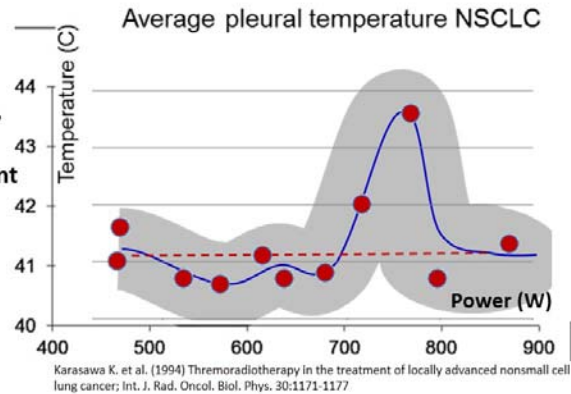
- ➡ **Temperature spreads!**
- It increases the blood-flow trying to compensate the heating.
- We need blood-flow for complementary therapies
 - radio [blood-oxygen]
 - chemo [drug delivery]
- ➡ **Supply extra nutrients for tumor!**
- ➡ **Dissemination is highly possible!**

The blood-flow is not controlled, it intensifies at the most proliferating boundary of the tumor!

Challenges of temperature



Blood-compensates, tries keeping the temperature constant

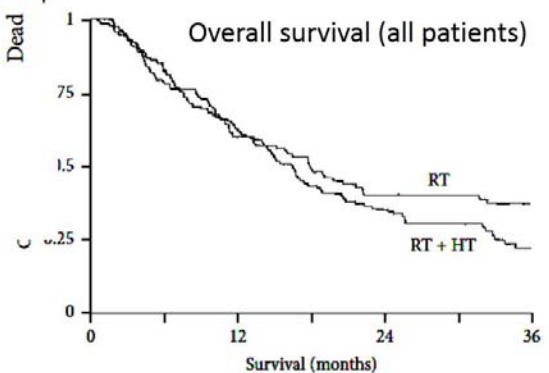
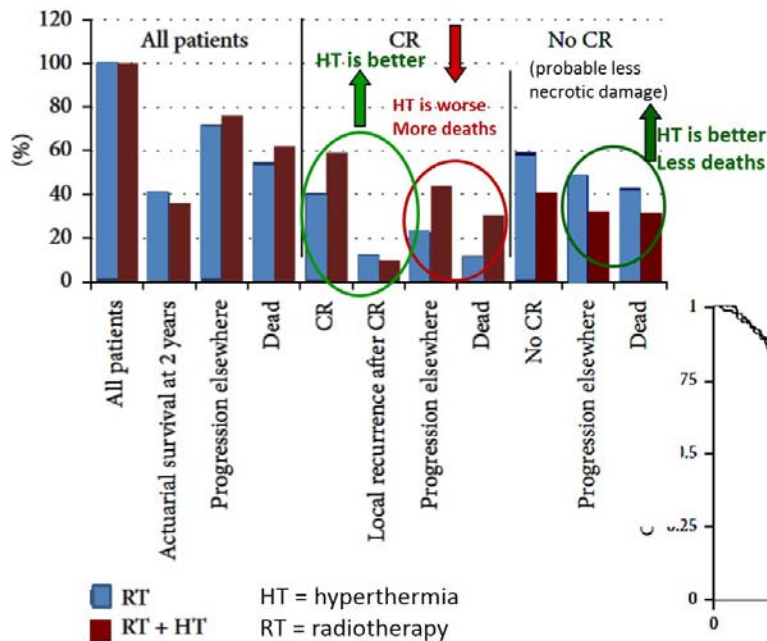


Hot- and cold-spots produce different temperatures at the same incident power

Challenges with clinical results (local hyperthermia)

Breast study (superficial) (England/Netherlands)

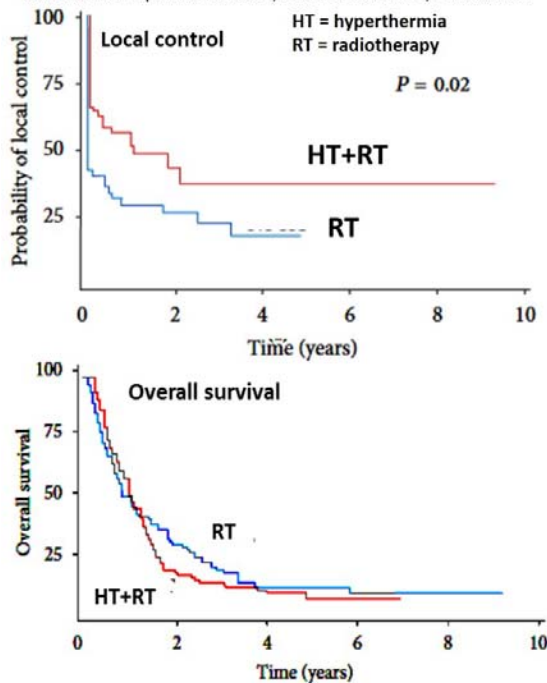
C. C.Vernon, J.W.Hand, S. B. Field et al., "Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials," *International Journal of Radiation Oncology Biology Physics*, vol. 35, no. 4, pp. 731-744, 1996.



Challenges with clinical results

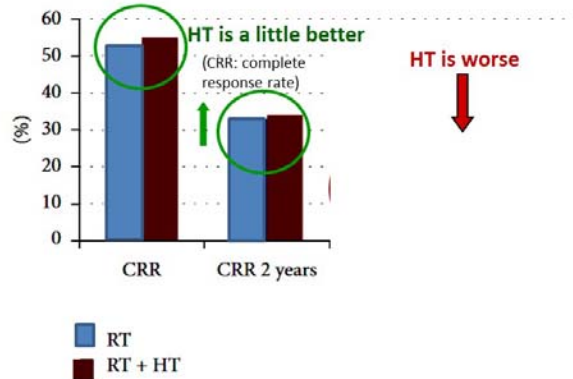
Superficial tumors study (USA) (RT+HT)

Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vujaskovic Z, Yu D, Sanders LL, Dewhirst MW. Randomized trial of hyperthermia and radiation for superficial tumors; *J Clin Oncol*. 2005; 23:3079-85



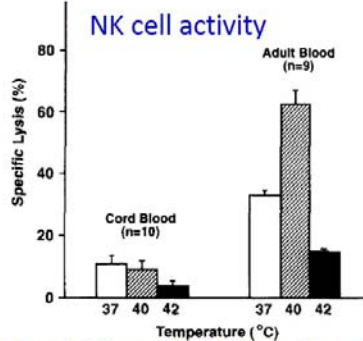
Toxicity study

B. Emami, C. Scott, C. A. Perez et al., "Phase III study of interstitial thermoradiotherapy compared with interstitial radiotherapy alone in the treatment of recurrent or persistent human tumors: a prospectively controlled randomized study by the radiation therapy oncology group," *International Journal of Radiation Oncology Biology Physics*, vol. 34, no. 5, pp. 1097-1104, 1996



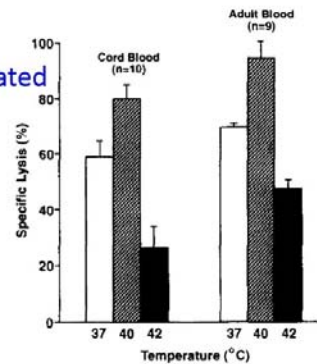
Temperature over 40°C suppresses the immune-cell- activity

Shen R-N et.al: (1994) *Int. J. Radiation Oncology Biol. Phys.*, 29: 821-826

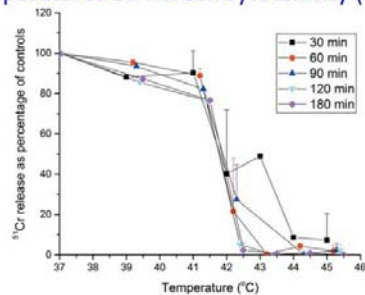


Lymphocyte-activated killer cell activity

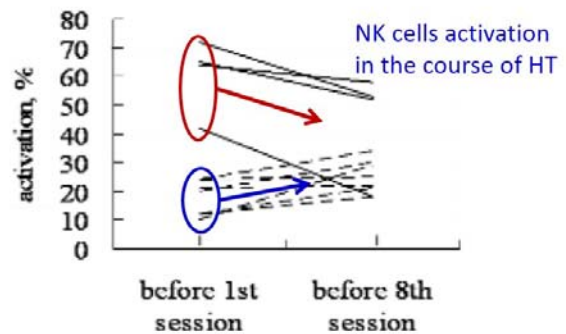
Newer support of the observations:
Beachy SH, Repasky EA: (2011) *Int J Hyperthermia*. 27:344-352



The effects of different incubation times and temperatures on NK cell cytotoxicity (n=2-27)



Hietanen T et al. Restoring Natural Killer Cell Cytotoxicity After Hyperthermia Alone or Combined with Radiotherapy, *ANTICANCER RESEARCH* 36: 555-564 (2016)



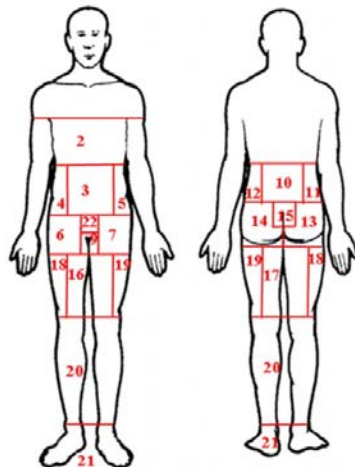
Ostapenko VV et al. Immune-related Effects of Local Hyperthermia in Patients with Primary Liver Cancer, *Hepato-Gastroenterology* 2005; 52:1502-1506

Challenges in patient's complains

35 treated patients

70 treatments

935 complains



Predefined complaint regions

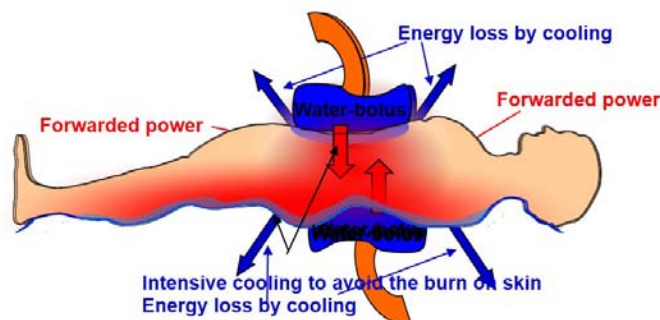
Region (regions as in figure 2)	Complaint occurrence (%)	Average DTC ($\pm$ SE)
Abdomen mid	27.6	3.5 ± 0.1
Lower back mid	18.8	3.2 ± 0.1
Tailbone/anus	8.0	2.1 ± 0.2
Buttocks left	7.9	4.9 ± 0.2
Buttocks right	6.4	5.7 ± 0.2
Vagina/perineum	6.3	1.4 ± 0.2
Pubic bone	4.3	1.9 ± 0.2
Groin/Hip right	3.5	7.9 ± 0.3
Bladder	3.2	2.8 ± 0.2
Groin/Hip left	3.1	7.4 ± 0.3
Abdomen left	3.0	5.7 ± 0.7
Abdomen right	1.4	5.5 ± 0.5
Lower back left	1.1	6.9 ± 0.4
Thigh left	0.9	$9.0 \pm 0.1.6$
Legs	0.7	NaN (outside HTP models)
Stomach/upper abdomen	0.7	9.7 ± 1.3
Feet	0.5	NaN (outside HTP models)
Thigh right	0.4	7.7 ± 3.0
Thigh top	0.3	10.8 ± 0.8
Systemic	0.3	NaN (no fixed region)
Lower back right	0.1	7.4 (no SE, single complaint)

Distribution of the occurrence of complains in all regions, and corresponding DTC values. (DTC = distance of complaint)

Canters RAM, Franckena M, van der Zee J, van Rhoon GC, Optimizing deep hyperthermia treatments: are locations of patient pain complains correlated with modelled SAR peak locations? Phys. Med. Biol. 56 (2011) 439–451

Challenges with techniques

➤ Surface cooling



The uncontrolled loss of energy **blocks the normal dosing**,
it cannot be measured by the incident energy (J/kg),
 (as it is usual in radiotherapy)

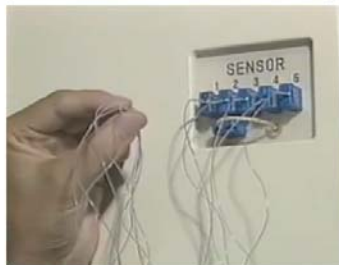
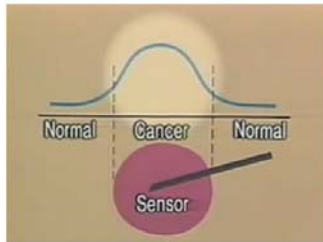
Measurement of the temperature
could be the basic of the dose only.

Challenges with techniques

➤ Temperature measurement and its problems

Conventional temperature measurements

- Infrared radiation (measures the surface only)
- Radiometry (near surface measurement and very inaccurate)
- MRI (inaccurate, very expensive)
- Invasive temperature measurements (point-sensor, complications)



Complications could be

- inflammation
- ulcerous wound
- infection
- internal bleeding
- risk of metastases

Challenges with techniques

Instead of commercial RF-technology, a specialized modern electronics developed for the special tasks is requested



Understanding that the applied devices are decisional, they make different bio-electromagnetic effects

Challenges with techniques

No shielding is necessary
for medical frequencies:

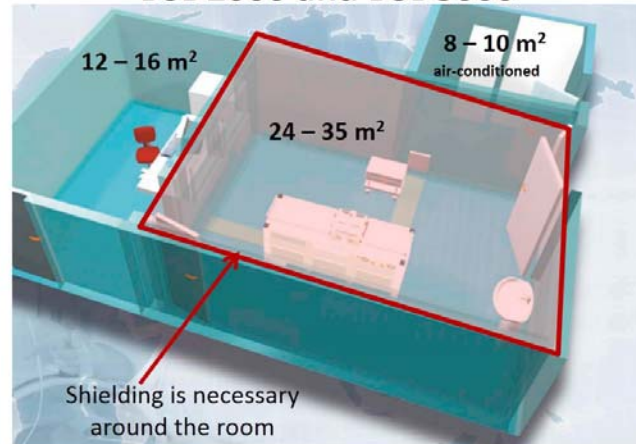
13.56 MHz $\pm$ 6.68 kHz
27.12 MHz $\pm$ 160.00 kHz
40.68 MHz $\pm$ 20.00 kHz
915 MHz $\pm$ 13 MHz
2450 MHz $\pm$ 50 MHz
5800 MHz $\pm$ 75 MHz
24125 MHz $\pm$ 125 MHz

The shielding and the operational
cost of the device itself is expensive

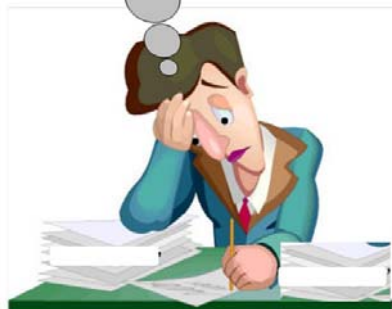
Thermotron RF-8 (8 MHz)



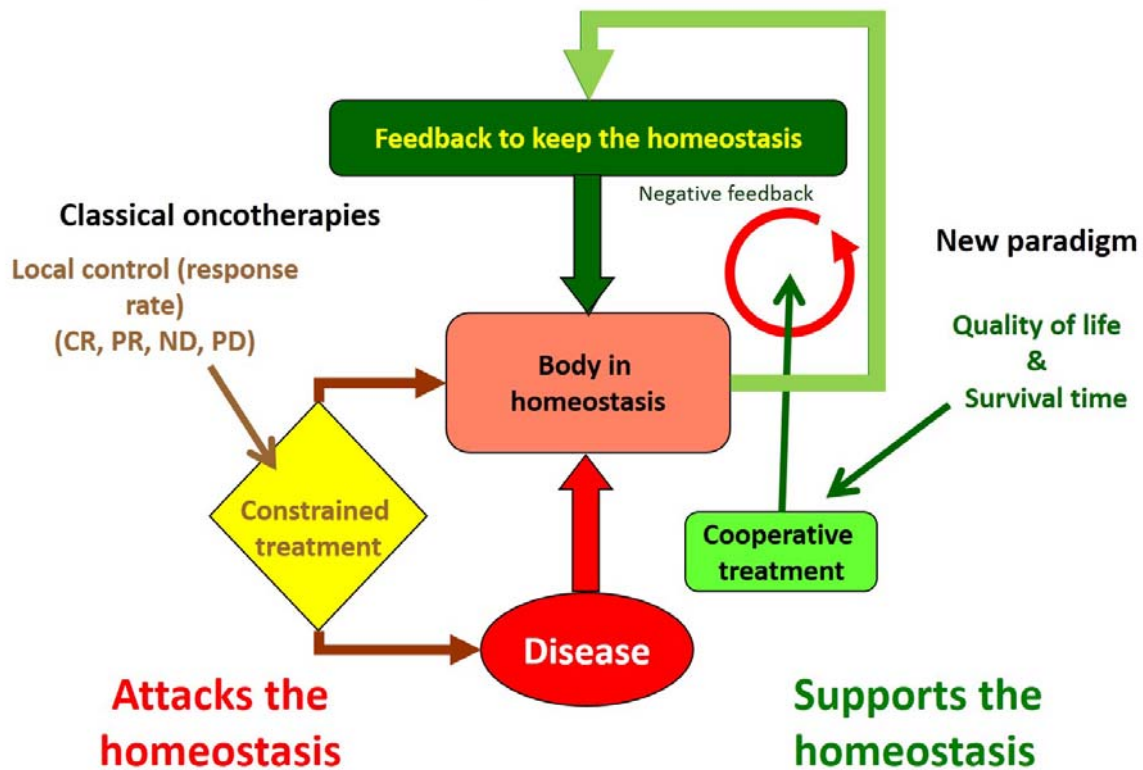
BSD2000 and BSD3000



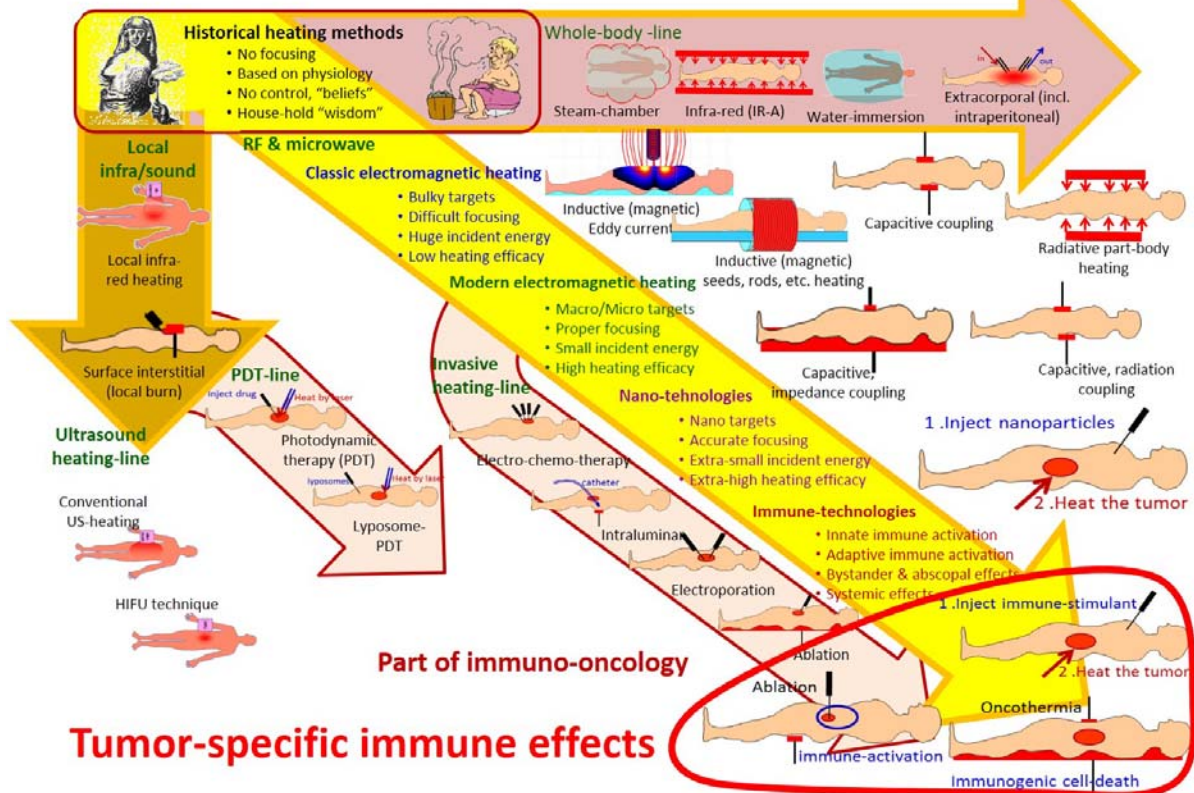
To treat or not to treat?
To heat or not to heat?
To choose or not to choose?



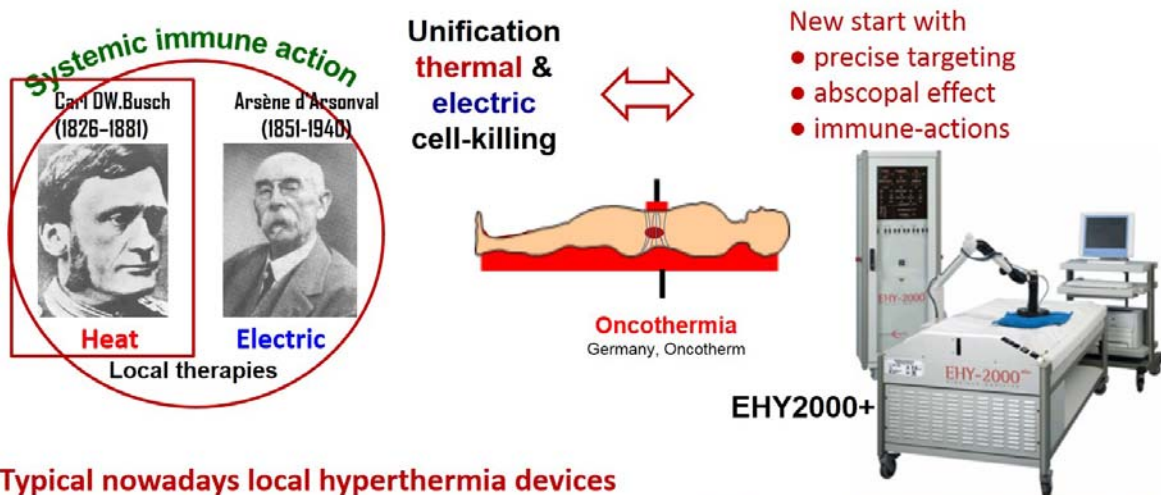
Change of paradigm in therapies



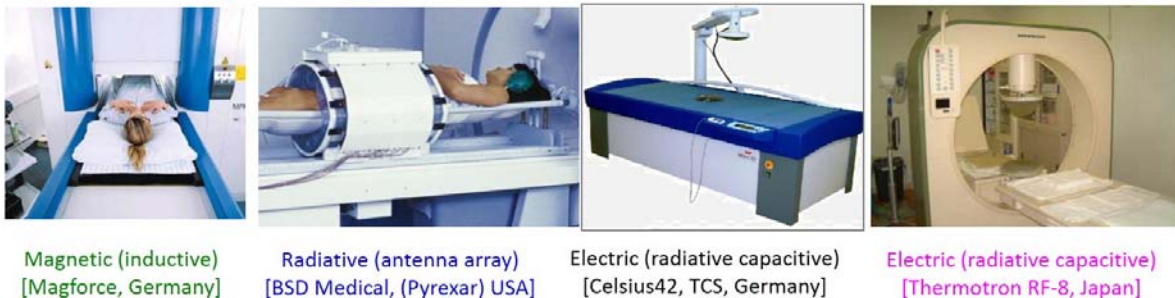
Hyperthermia methods



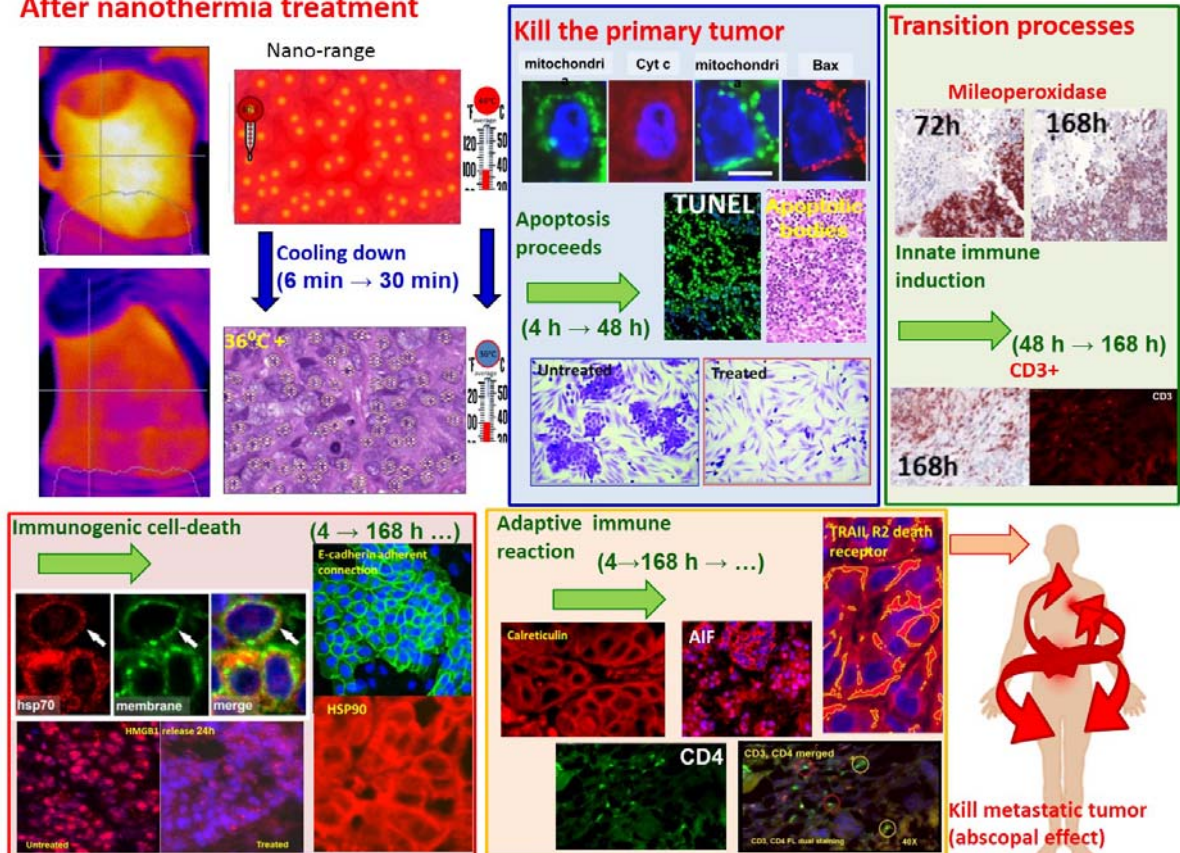
New approach in oncologic hyperthermia



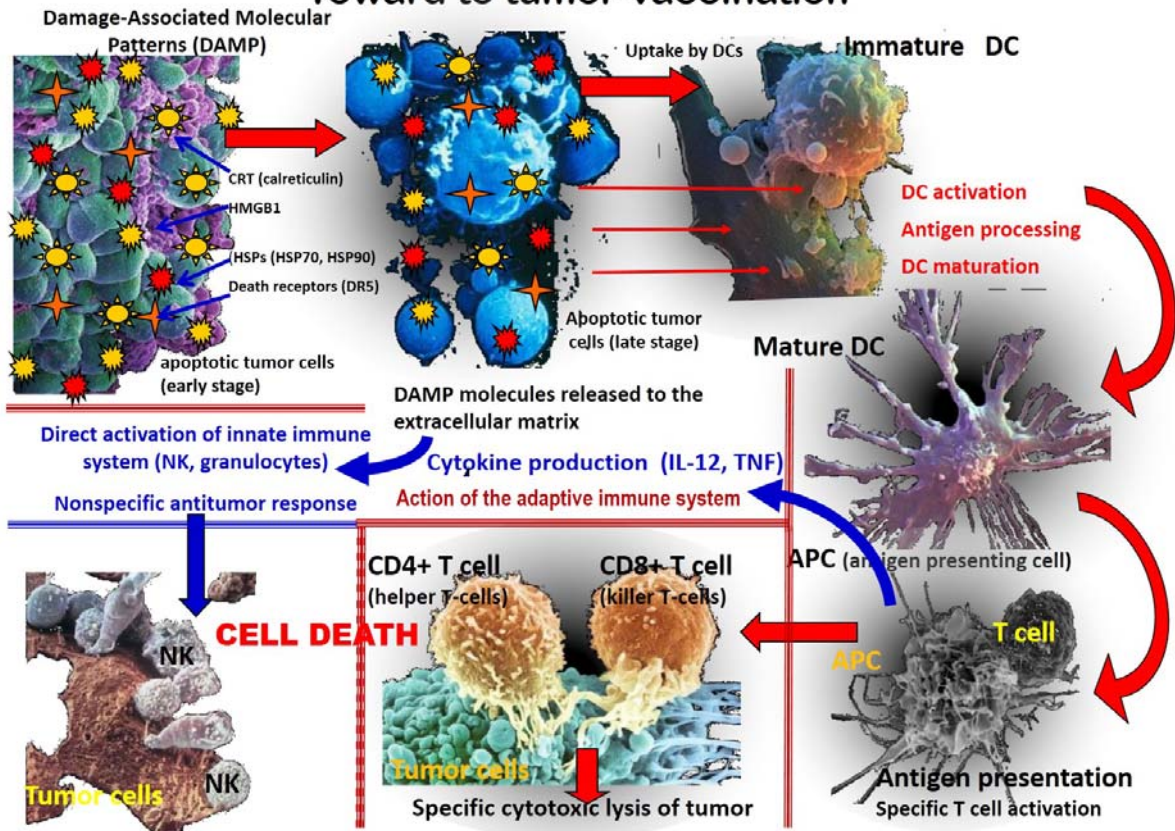
Typical nowadays local hyperthermia devices



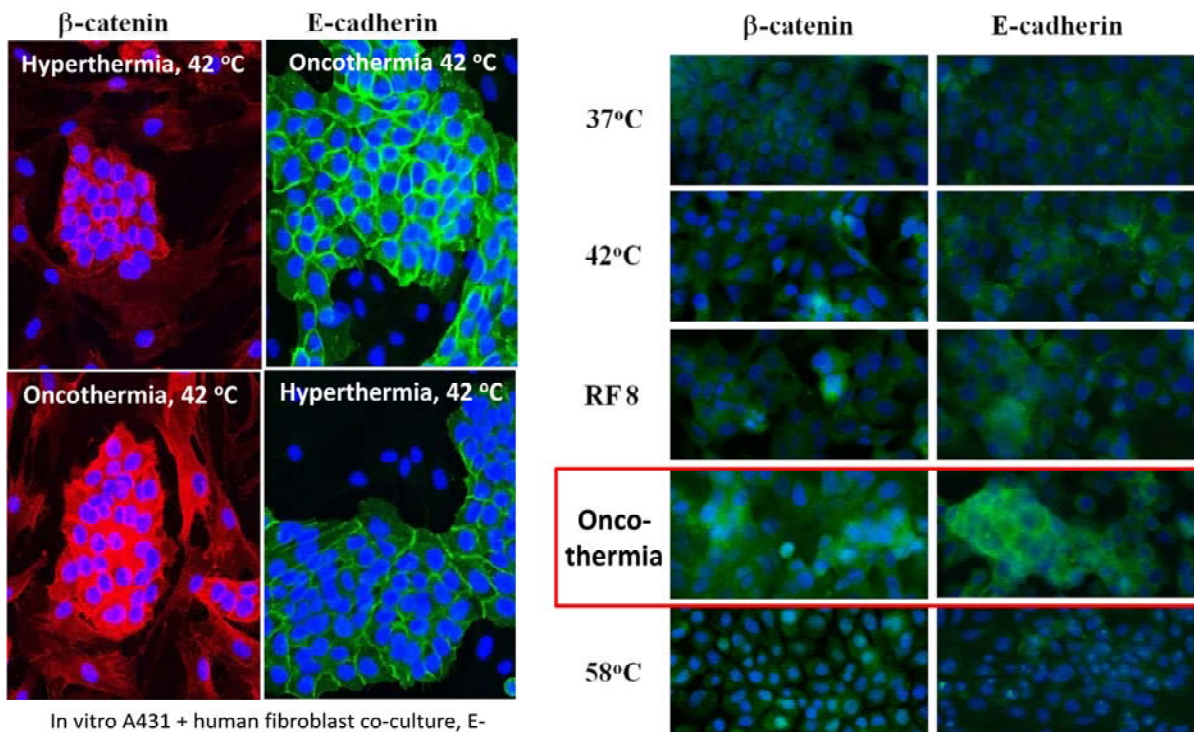
After nanothermia treatment



Toward to tumor-vaccination

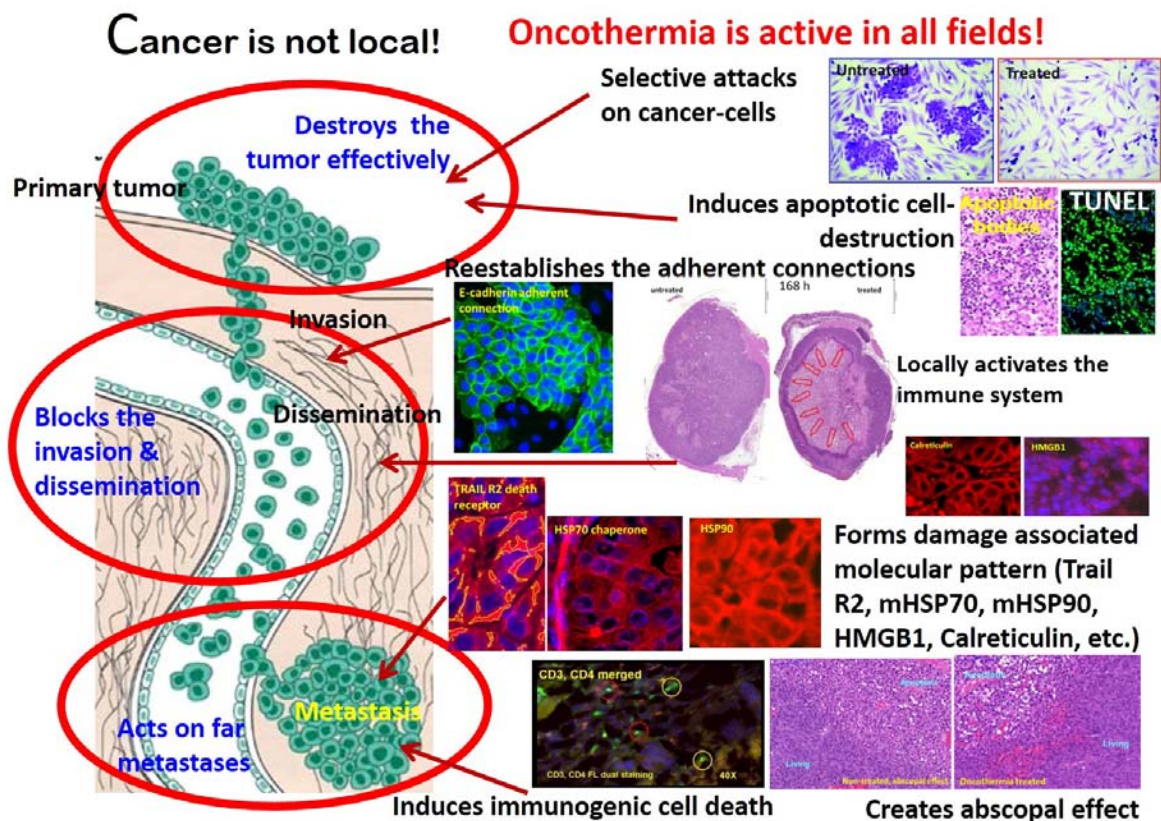


Block the invasion and dissemination



Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165

Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et.al. (2016) In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, oi: 10.18632/oncotarget.11444



Change of Paradigm of Hyperthermia in basic effects

Old Paradigm	New Paradigm
Induces high blood-flow, supports the growth of tumor and risks metastases	Should be selective , must not gain the contra-effective blood-flow, only mild
Aims necrosis killing the tumor. Minor apoptosis happens through internal signal-path (mitochondria)	Should kill the malignant cells by apoptosis . Apoptosis happens through external (membrane) signal path
Breaks the intercellular junctions	Should reestablish the intercellular junctions
Intervenes in homeostatic control	Should support homeostatic control
Blocks immune cells by excess heat-energy, with too high temperature	Should activate immune cells for immunogenic cell-death
Has high heat-toxicity risk by excess heat-energy	Should have low risk by controlling energy dose
Forces to pursue absolute degree of temperature of tumor as a whole	Should produce igniting effect of temperature on membrane of tumor cell
Concentrates on local tumor control	Should be centered on the systemic tumor control (abscopal effect)

Change of Paradigm of Hyperthermia in clinical practice

Old Paradigm	New Paradigm
Measures the temperature for control	The temperature measurement is not necessary
Uses the CEM43°C Tx as dose	Uses energy -intake for dose
Complicated to use, difficult to tune	Simple to use, automatically focuses on the actual malignancy
Concentrates on the local tumor only	
Has thermal damages and thermal toxicity	Has no thermal toxicity
Does not control the distant metastases	Controls the metastases by abscopal effect (tumor-specific immune reaction)
Has no effective focusing on malignant cells	Effectively selects the malignant - cells in the heterogeneous tumor
No consideration on the physiologic feedbacks of the patient	Takes the physiological feedback into account
Relatively high price/benefit ratio	Relatively cheap with high benefit

The new paradigm needs new thinking



Thank you for following my talk

Take home message

In contrary that the hyperthermia was the very first treatment in oncology it is not widely accepted. It is in childhood yet!

We need new paradigm!

Never treat the tumor alone!

Treat the PATIENT who has tumor!



Take complexity into consideration, use the update advantages of immuno-oncology!

Conventional hyperthermia
high overall power

complete (mass) heating strategy
CEM43⁰CT_x, local control,
kill the cells by constrain heat

Oncothermia high nano-range
targeted power

selective (nano) heating strategy
survival time & QoL
"teach" the system how to kill

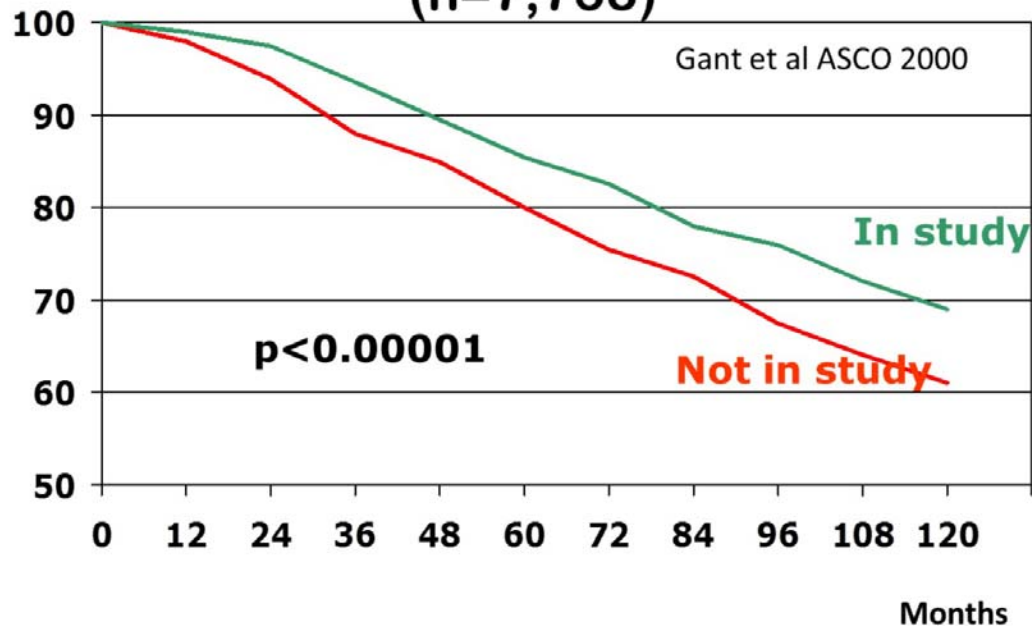
Nobel-prize for Traditional Chinese Medicine (2015)



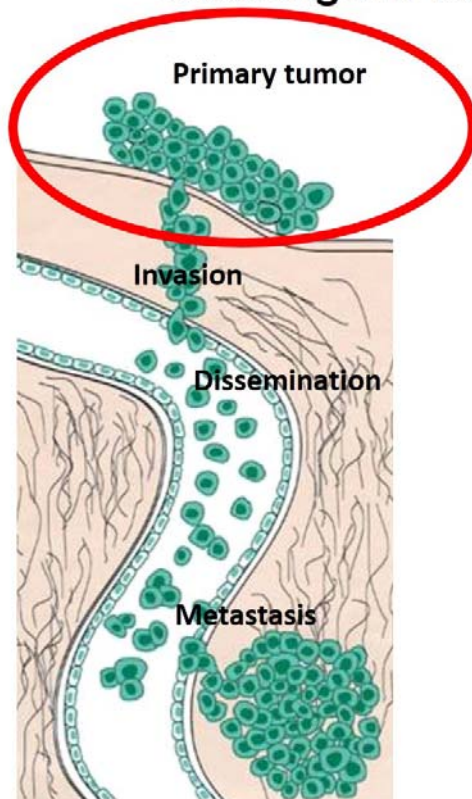
Challenge in prospective studies

Challenge in prospective studies

Overall survival of mammary carcinoma (n=7,738)



Challenge of targeting in oncology

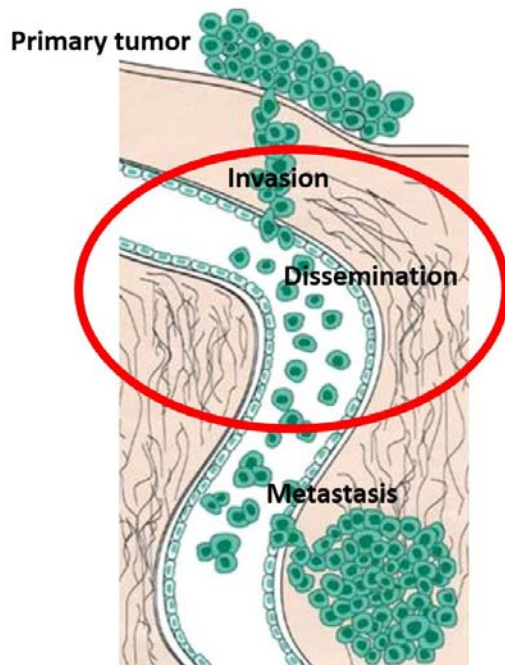


Which option do we have in refractory cases when the standard protocols fail?



Challenge of targeting in oncology

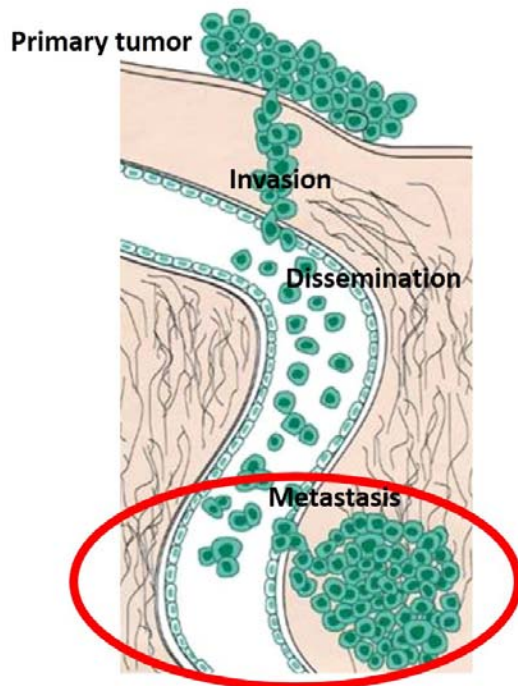
How to block the invasion and dissemination of malignant cells?



Malignancy looks local, but it isn't.

Challenge of targeting in oncology

What to do with metastases?



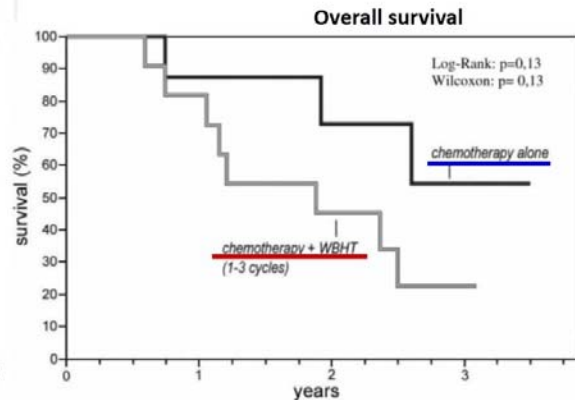
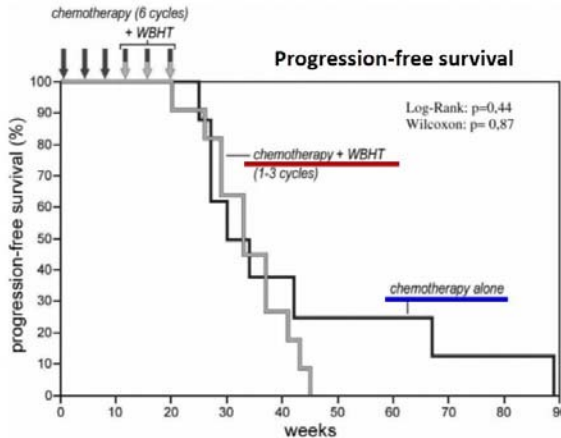
Challenges with clinical results (whole-body hyperthermia)

Metastatic colorectal cancer

(Phase I/II prospective double arm study)

B. Hildebrandt, J. Dräger, T. Kerner, M. Deja, J. Löffel, C. Stroszczyński, O. Ahlers, R. Felix, H. Riess, P. Wust. Whole-body hyperthermia in the scope of von Ardenne's systemic cancer multistep therapy (sCMT) combined with chemotherapy in patients with metastatic colorectal cancer: a phase I/II study; *Int. J. Hyperthermia*, 20:317–333 (2004)

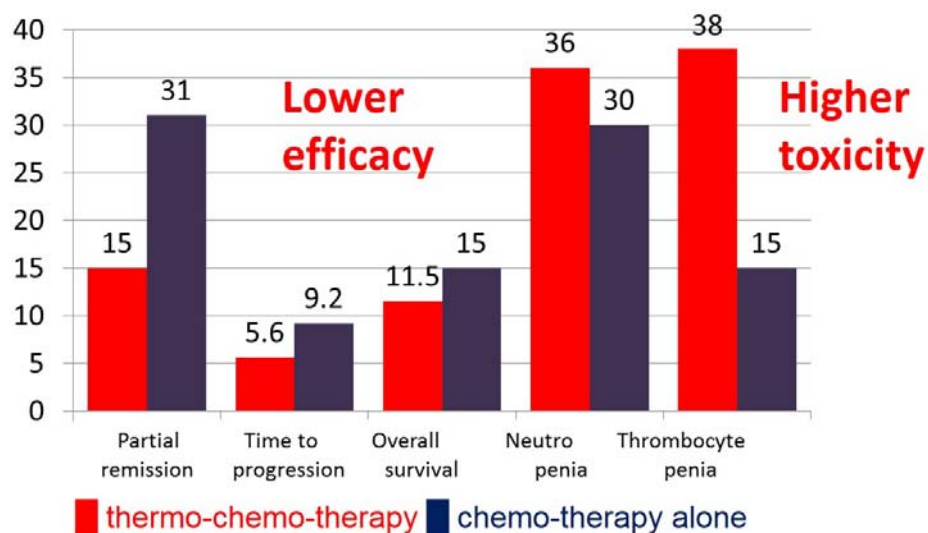
The heat-up time was defined as the time interval for heating the blood from 37.5 to 42.1 °C, and it could vary considerably (60–150 min). The plateau phase started by reaching a temperature of 41.8 °C in the aorta. It was kept stable for 60 min by properly adjusting the total power of the radiators, typically by reducing it to one-third of the initial power.



Progression-free survival for the two treatment groups in comparison. *Note that the graph does not represent a comparison of similar patient groups: all patients treated with sCMT plus chemotherapy previously had not responded to three courses of conventional chemotherapy. All patients treated with chemotherapy alone had a partial response after three courses.

Overall survival for the two treatment groups in comparison. *Note the graph does not represent a comparison of similar patient groups: all patients treated with sCMT plus chemotherapy previously had not responded to three courses of conventional chemotherapy. All patients treated with chemotherapy alone had a partial response after three courses.

Extreme whole-body hyperthermia effect (41-42°C)

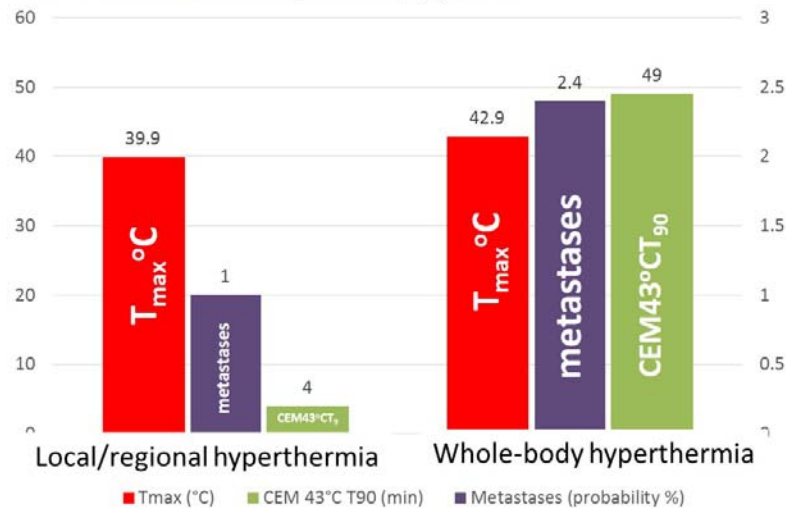


Bakhshandeh A, Wiedemann G, Zabel P, et al. Randomized trial with ICE (ifosfamide, carboplatin, etoposide) plus whole body hyperthermia versus ICE chemotherapy for malignant pleural mesothelioma. *Journal of Clinical Oncology*, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: 7288.

Extreme (40-42°C) whole-body hyperthermia worsened the effect of conventional treatment

Whole-body and local-regional hyperthermia effect

Thrall DE, et al. Radiation plus local hyperthermia versus radiation plus the combination of local and whole-body hyperthermia in canine sarcomas. Int J Radiat Oncol Biol Phys. Mar 1996;34(5):1087-96.



CONCLUSION: The combination of LH + WBH with radiation therapy was not associated with an increase in local tumor control in comparison to use of LH with radiation therapy. The combination of LH + WBH also appeared to alter the biology of the metastatic process and was associated with more complications than LH. **We identified no rationale for further study** of LH + WBH in combination with radiation for treatment of solid tumors.

Challenges of the market

The conventional hyperthermia methods had lost their “attractive behavior”, and they are abandoned in many University places.

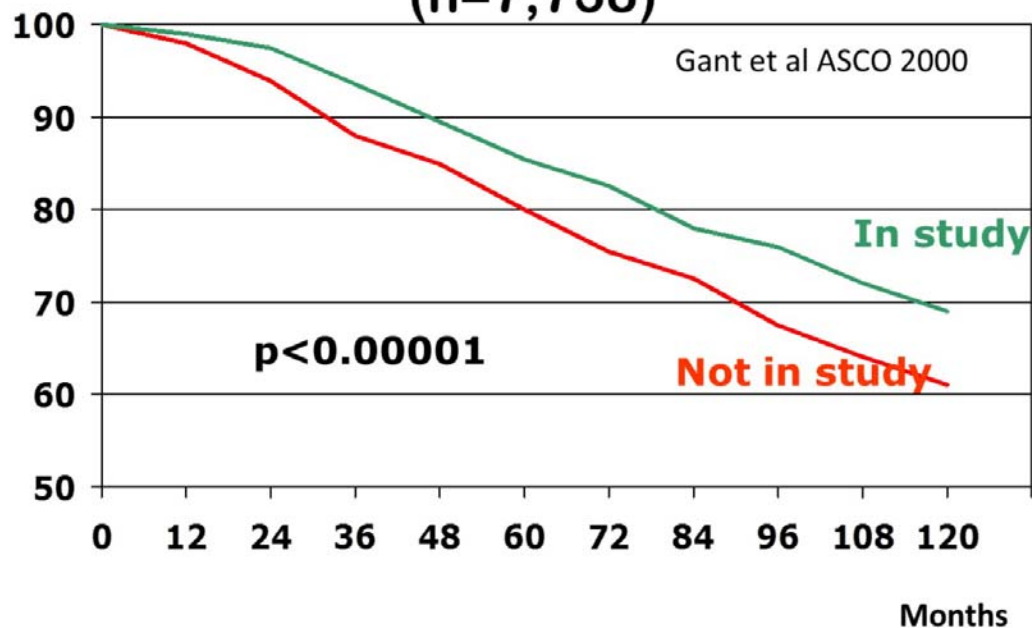
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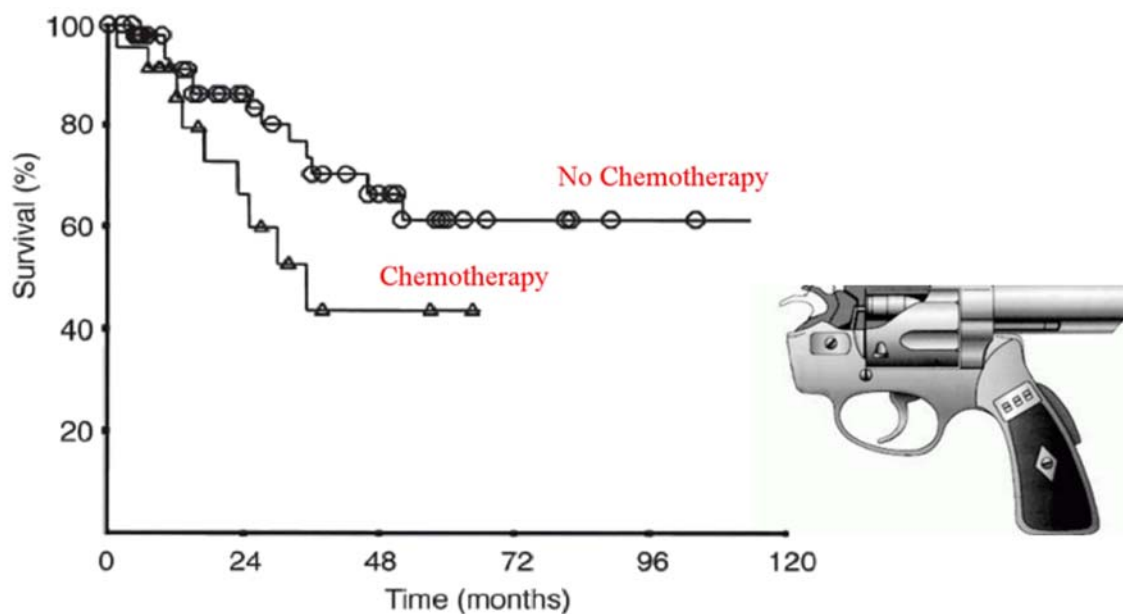


Challenge in prospective studies

Overall survival of mammary carcinoma (n=7,738)



Controversies in chemotherapy

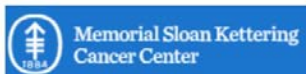
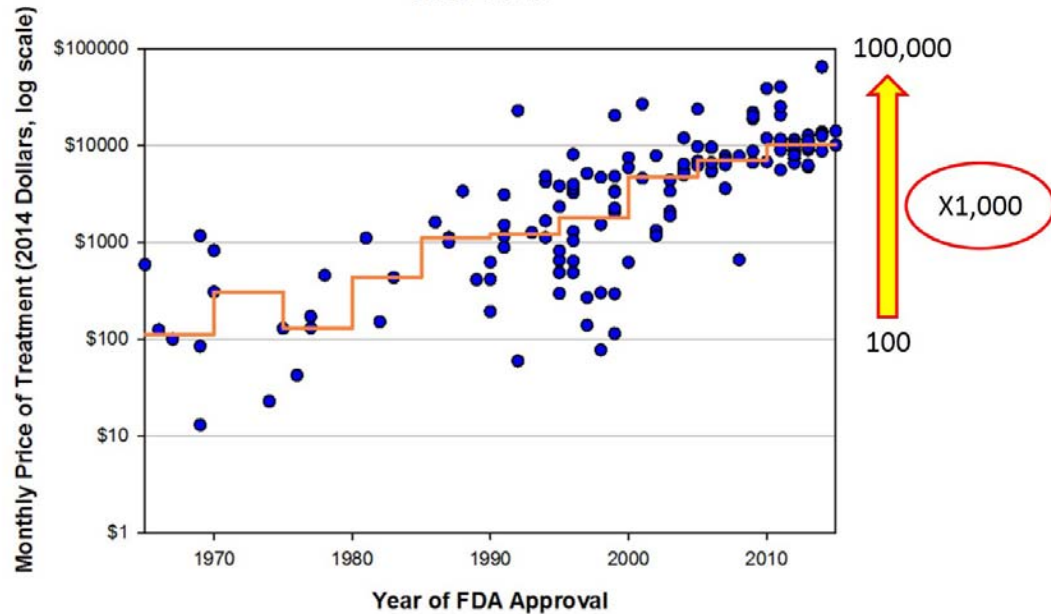


Comparison of disease-specific survival in patients with lymph node disease who either received (23 patients) or did not receive (53 patients) chemotherapy.

Adapted from Allen, 2005. <http://www.merkelcell.org/treatment/>

Challenge of financing of chemotherapy

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965 - 2015

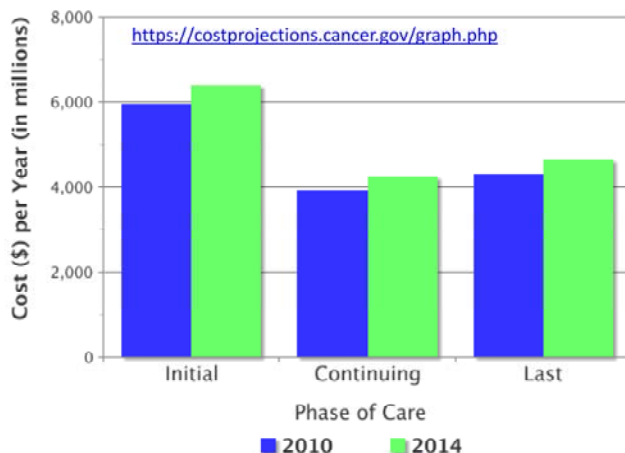


<https://www.mskcc.org/profile/peter-bach>

Example: cost of chemotherapy for colorectal cancer

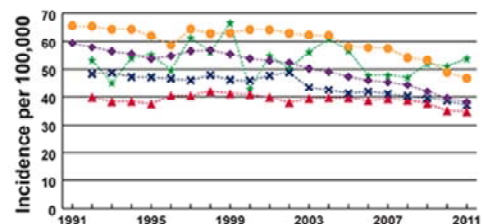
•1990	97 x 6 months	582 €
•1996	143 x 6 months	1716 €
•2003	729 x 6 months	8448 €
•2004	1224 x 6 months	14688 €
•2010	5000 x 6 months	60000 €

Cost of Cancer Care by Phase of Care, Colorectal, All Ages, Male and Female, in 2010 Dollars

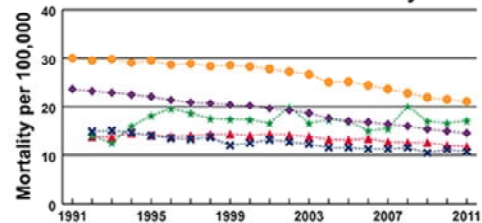


Assumptions:
Incidence - Constant (2003 - 05 average rate)
Survival - Constant (2005 rate)
Cost Increase - 0% per year
Source: <https://costprojections.cancer.gov>

U.S. Colorectal Cancer Incidence



U.S. Colorectal Cancer Mortality



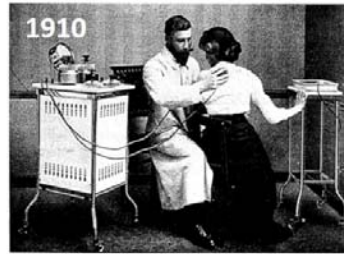
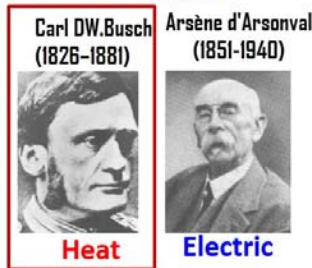
◆ Whites ◆ African Americans ◆ Hispanics*
◆ Asians/Pacific Islanders* ◆ American Indians/Alaska Natives*

*Incidence and mortality data not available before 1992.

<http://www.cancer.gov/research/progress/snapshots/colorectal>

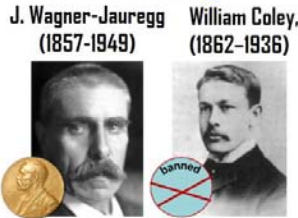
Historic approach in oncologic hyperthermia

Local therapies



Whole-body therapies

Internal inducing

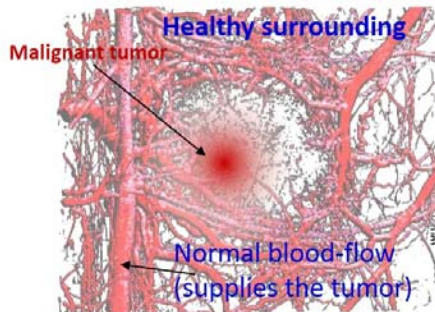


External inducing

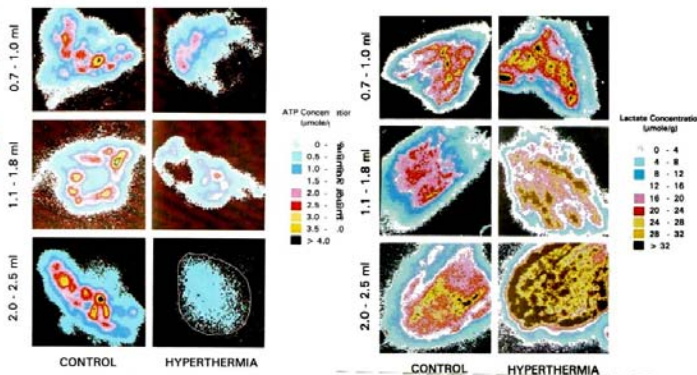


The oldest medical therapy: thermo-therapy

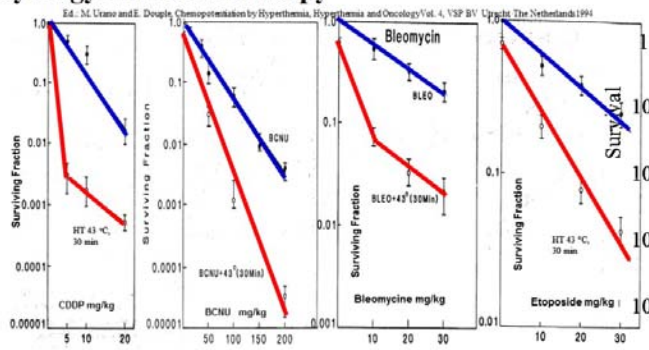
Vaupel PW, Kelleher DK: 1995



Local heating →
intensifies the metabolism, without extra supply → **burning out**



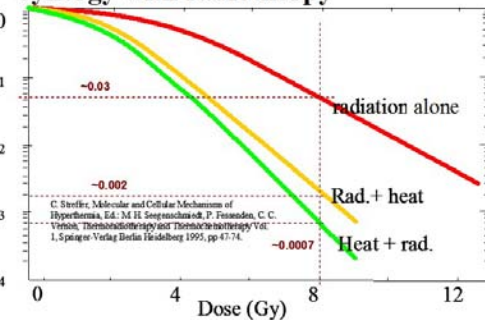
Synergy with chemotherapy



ATP decreases; deprivation of energy

Lactic acid formation; acidosis

Synergy with radiotherapy



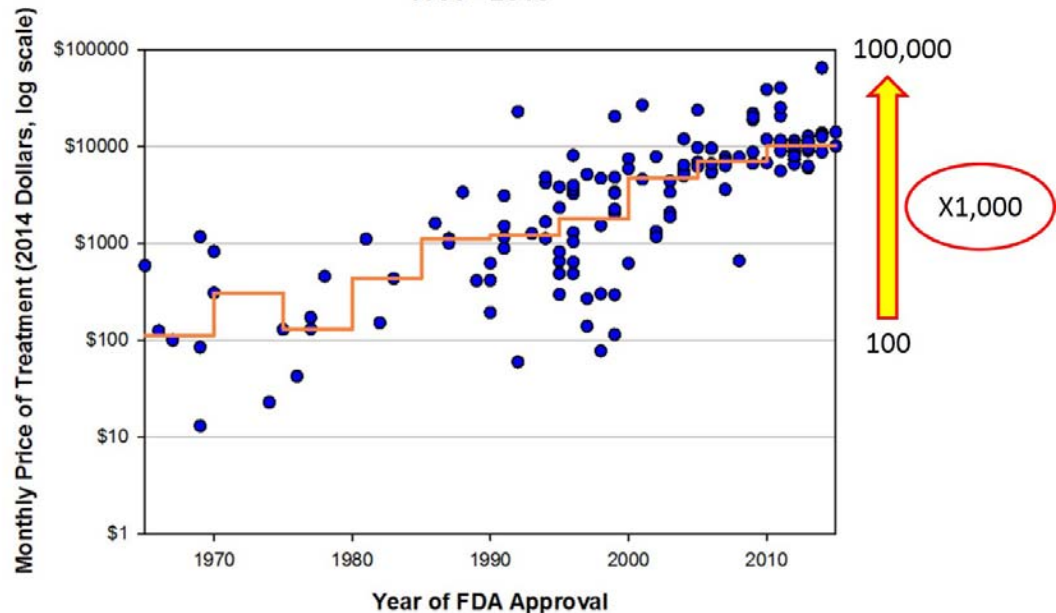
The heating in laboratory experiments is perfect



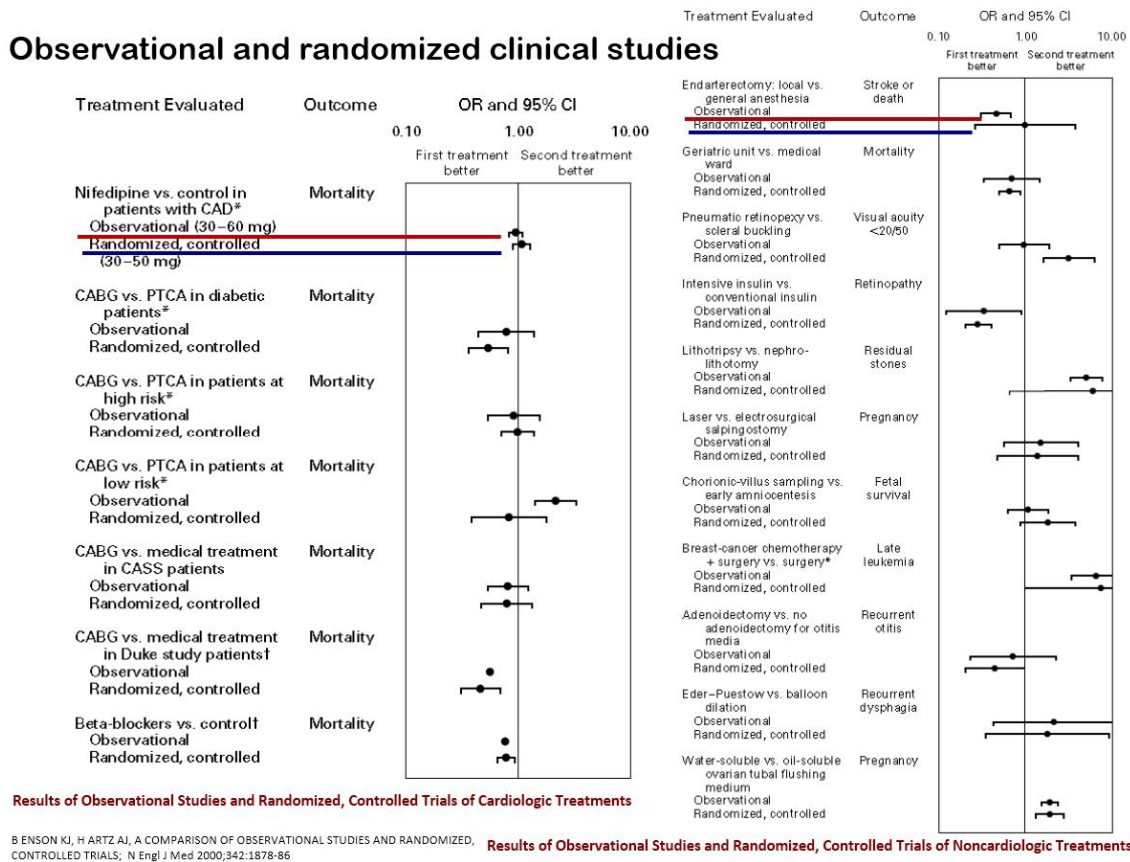
When he would be mouse we could completely cure him...

Challenge of financing of chemotherapy

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965 - 2015

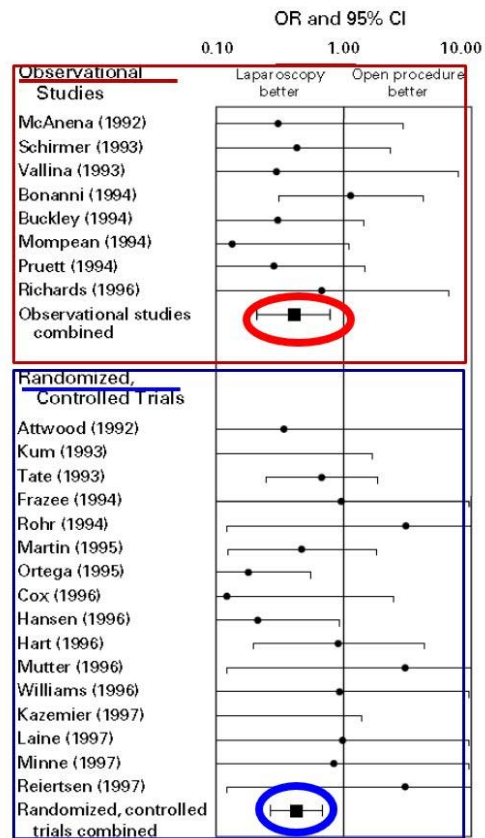


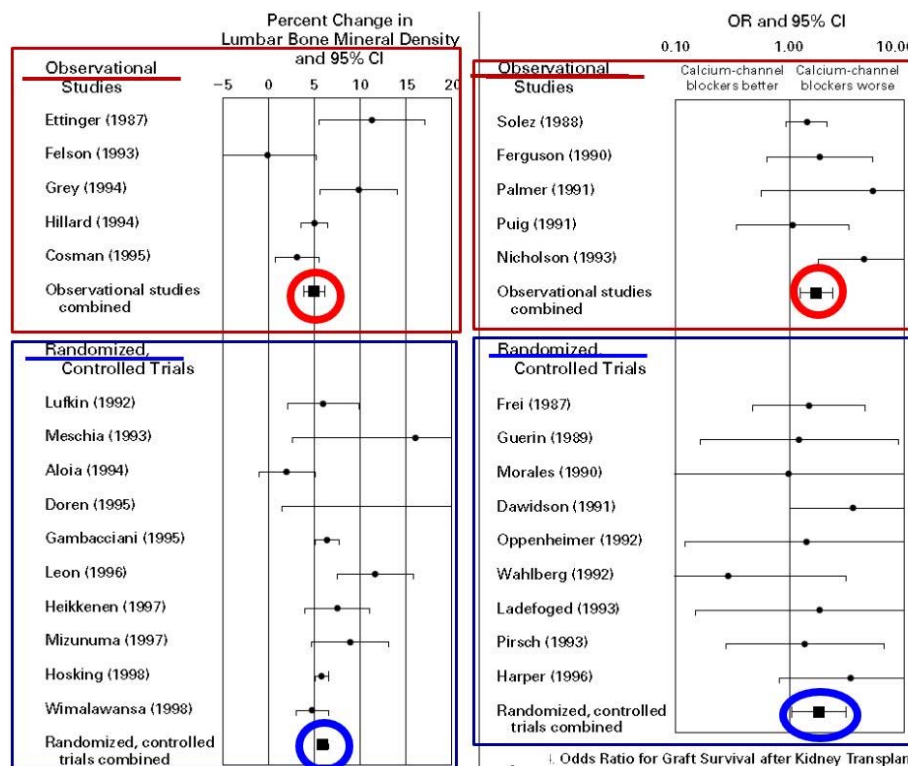
Observational and randomized clinical studies



Odds Ratio for Infection after Laparoscopic as Compared with Open Appendectomy

B ENSON KJ, H ARTZ AJ, A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS; N Engl J Med 2000;342:1878-86





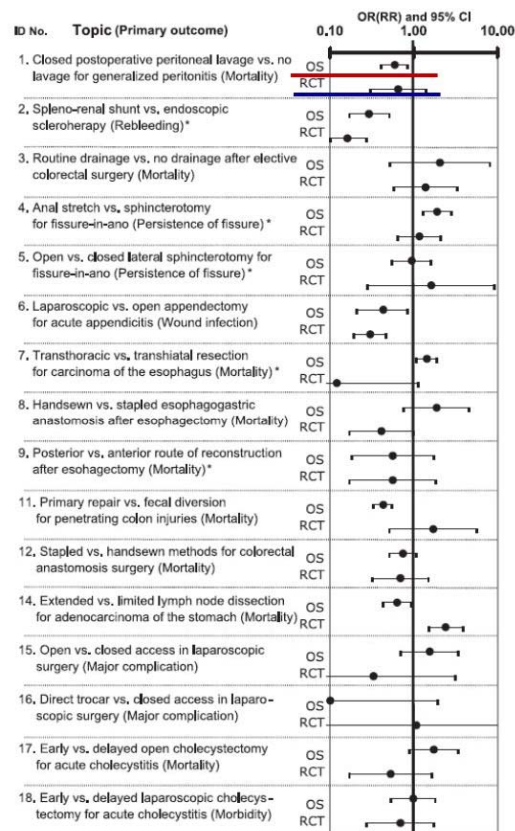
Percent Change in Lumbar Bone Density in Postmenopausal Women Given One to Two Years of Hormone-Replacement Therapy as Compared with Controls.

Odds Ratio for Graft Survival after Kidney Transplantation in Patients Receiving Calcium-Channel Blockers as Compared with Controls.

The figure is based on data from six articles⁵⁸⁻⁶³. The nine randomized, controlled trials were analyzed by Ladefoged and

Comparison of primary outcomes between observational studies and randomized controlled trials. This figure is based on data from 13 review articles 7,18–24,26,27,29–31 and 10 meta-analyses of observational studies by the authors. OR, odds ratio; RR, relative risk; CI, confidence interval.
*Outcome reporting relative risk rather than odds ratio.

Shikata S et al; Comparison of Effects in Randomized Controlled Trials With Observational Studies in Digestive Surgery; Ann Surg 2006;244: 668–676



Combining hyperthermia with other anticancer methods

Dr. Joseph Brenner

“New-Hope” Integrative Oncology Center, Tel-Aviv/Israel

Combining hyperthermia with other anticancer methods

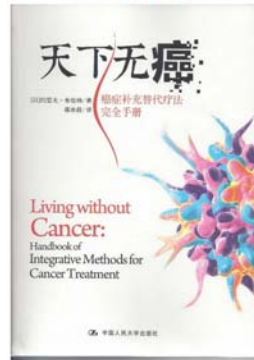
Dr. Joseph Brenner
“new-Hope”
Integrative oncology center
Tel-Aviv/Israel

Opening ceremony of “New-Hope” clinic
1997



TEXTBOOK FOR INTEGRATIVE ONCOLOGY

CHINEESE



HEBREW/ENGLISH/RUSSIAN



**You need more than 2
hands to pull a car out
of the mud**

**You need more than
one treatment method
to fight cancer**



HYPERTHERMIA IS AN EXCELLENT • NON-TOXIC ANTI-CANCER METHOD THAT SHOULD BE A PART OF THE TREATMENT OF ALMOST ANY CANCER PATIENT, WITH OR WITHOUT OTHER TREATMENT METHODS

Combining hyperthermia

- With conventional methods:
 - Surgery
 - Chemotherapy
 - RT
 - Hormones
 - Biologics
 - Hyperbaric oxygen
 - PDT
- With integrative oncology methods:
 - Different types of hyperthermia
 - Supplements
 - IVC

Hyperthermia and Surgery



Pre-operative hyperthermia

Hyperthermia may be a part of neoadjuvant preoperative treatments.

Aim is to reduce tumor size for a better surgery and prevent tumor cells spread during the operation.

The question: how many days before surgery should we stop the HT?

Case report: A 55 Y.O male with pancreatic cancer. HT was given 3 weeks before a Whipple surgery by a daily treatments until 3 days before surgery.

According to surgeon, surgery was very difficult due to very loose tissues.

Patient is alive and well today 6 years later.

Esophageal Cancer: Neoadjuvant Hyperthermo-Chemoradiotherapy

- Department of General Surgical Science (Surgery I), Gunma University, Graduate School of Medicine, Maebashi 371-8511, Japan.
- [Hepatogastroenterology](#). 2015 Jun;62(140):887-91.

- Results of neoadjuvant hyperthermo-chemoradiotherapy (HCRT) using weekly low-dose docetaxel followed by surgery in patients with advanced esophageal squamous cell carcinoma.
- In the 24 patients, the response rate was 41.7%.
- The 3- and 5-year survival rates were 56.3% and 50.0%, respectively.
- **CONCLUSIONS:** Esophagectomy after docetaxel HCRT may have potential for prolonging survival in patients with locally advanced esophageal cancer.

Rectal Cancer: Preoperative radiochemotherapy in combination with deep regional hyperthermia

Department of Radiation Oncology, University Hospital Tuebingen, Hoppe-Seyler-Strasse 3, Tuebingen, Germany • [Int J Hyperthermia](#). 2016;32(2):187-92

- A randomized study
- In total 103 patients with **locally advanced non-metastatic rectal cancer** were treated preoperatively with either neoadjuvant radiochemotherapy alone (n = 43) or the same treatment with additional deep regional hyperthermia (n = 60)
- **RESULTS:** Patients receiving additional hyperthermia had excellent 5 years local of 98% compared with 87% in the radiochemotherapy only group.
- Five-year rates for OS (88% versus 76%), DFS (77% versus 73%).
- **CONCLUSION:** Radiochemotherapy combined with hyperthermia resulted in excellent long-term local control

Combining different hyperthermia devices

Locally advanced breast cancer (refused surgery) treated with EHY-3000 to the whole chest and superficial hyperthermia

Before treatments



After treatments



Hyperthermia and Radiotherapy



Hyperthermia complements radiation:

Preventing radio-resistance

Hyperthermia is effective against radio resistant cells:
Cells in S-phase
Hypoxic cells
Low pH tissues

Hyperthermia prevent sub-lethal damage repair in the cancer cell through the effect on DNA repair enzymes.

Hyperthermia increases oxygenation of tumor cells rendering the tumor more radiosensitive

RT+Hyperthermia



Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis

- Center for Radiation Oncology KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland; Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland
[Int J Radiat Oncol Biol Phys.](#) 2016 Apr 1;94(5):1073-87

- Thermoradiation therapy enhances the likelihood of CR rates in locally recurrent breast cancers (LRBCs) over RT alone by 22%

For even those previously irradiated, reirradiation with HT provides locoregional control in two-thirds of the patients.

- Thermoradiation therapy could therefore be considered as an effective and safe palliative treatment option for LRBCs.

Local control rate after the combination of re-irradiation and hyperthermia for unresectable recurrent breast cancer: Results in 248 patients

- The Netherland group
[Radiother Oncol.](#) 2015 Nov;117(2):217-22

- We evaluated the efficacy and side effects in patients treated with re-RT and HT for irresectable locoregional breast cancer recurrences.
- The CR rate was 70%. at 1, 3, and 5 years LC was 53%, 40% and 39%.
- OS was 66%, 32%, and 18%, respectively. OS after 10 years was 10%.

Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial.

- The Netherlands group of radiotherapy and oncology hospitals
[Radiother Oncol.](#) 2016 Feb 17

- Chemoradiation (RT-CT) is standard treatment for locally advanced cervical cancer (LACC).
- Patients with locally advanced cervical cancer (LACC) were randomly assigned to RT-CT or RT-HT
- Data suggest comparable outcome for RT-CT and RT-HT.

Definitive radiotherapy plus regional hyperthermia for high-risk and very high-risk prostate carcinoma

- University of Occupational and Environmental Health , Kitakyushu , Japan.
[Int J Hyperthermia.](#) 2015;31(6):600-8

- Data from 82 patients treated with RT plus HT and 64 patients treated with RT alone were retrospectively analyzed.
- **CONCLUSIONS:** The addition of HT to RT may improve DFS for patients with high-risk or very high-risk prostate cancer.

HYPERTHERMIA AND CHEMOTHERAPY

- **Hyperthermia increases size of blood vessels** to the tumor allows more chemo to get inside the tumor.
- **Blood vessels outside of the tumor are narrowed** so chemo stays longer inside the tumor.
- **Hyperthermia delays the appearance of MDR (Multi-Drug-Resistance) .**

Chemotherapy and Hyperthermia



- **Synergistic effect** with doxorubicin, Doxil (pegilated liposomal doxorubicin), cisplatin and carboplatin, epirubicin, mitoxantron, mitomycin, BCNU, bleomycin, ifosfamid, cyclophosphamid, taxol, campto and gemzar.
- **Additive effect** with 5FU, vincristine, vinblastine and methotrexate.
- Delay MDR

Hyperthermia combined with chemotherapy for patients with residual or recurrent esophageal cancer after definitive chemoradiotherapy.

- Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan
[Anticancer Res.](#) 2015 Apr;35(4):2299-303.
- Salvage HCT after dCRT was performed in 11 patients with residual or recurrent oesophageal cancer.
- Complete response and stable disease was achieved in three and five patients, respectively; symptoms were improved in the remaining three patients.
The median survival time after HCT was 12 (range=3-88) months.

Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: A systematic review with conventional and network meta-analyses

- Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau , Aarau , Switzerland and Department of Radiation Oncology , University Hospital Zurich
[Int J Hyperthermia.](#) 2016 Jul 13:1-34.
- Comparing HTCTRT, HTRT, CTRT and RT alone was conducted.
- The pairwise comparison of various groups showed that HTRTCT was the best option for both CR and patient survival.

Effectiveness of Regional Hyperthermia With Chemotherapy for High-Risk Retroperitoneal and Abdominal Soft-Tissue Sarcoma After Complete Surgical Resection

- Department of General, Visceral, Transplantation, Vascular, and Thoracic Surgery, University of Munich—Campus Grosshadern, Munich, Germany. EORTC trial. [Ann Surg. 2014 Nov; 260\(5\): 749–756.](#)
- To determine whether regional hyperthermia (RHT) in addition to chemotherapy improves local tumor control after macroscopically complete resection of abdominal or retroperitoneal high-risk sarcomas
- 149 patients were identified with macroscopic complete resection (R0, R1) of abdominal and retroperitoneal soft-tissue sarcomas (median diameter 10 cm)
- Seventy-six patients were treated with EIA (etoposide, ifosfamide, doxorubicin) + RHT versus 73 patients receiving EIA alone.
- In patients with macroscopically complete tumor resection, RHT in addition to chemotherapy resulted in significantly improved local tumor control and DFS.

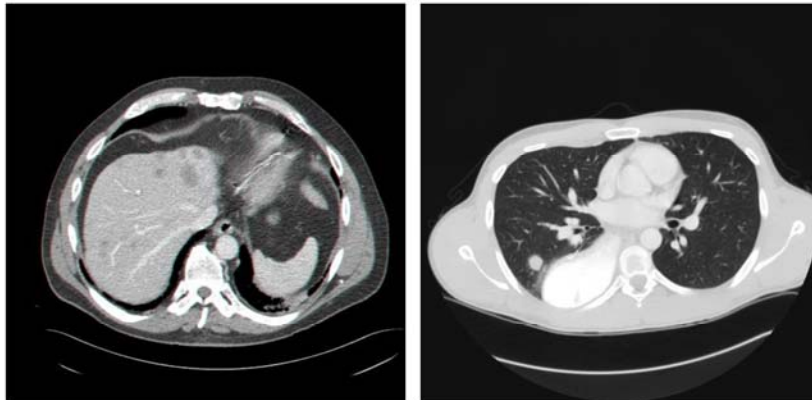
Combining Mitomycin C and Regional Hyperthermia in Patients with Nonmuscle Invasive Bladder Cancer

- Departments of Radiation Oncology and Urology (TMdR, JdIR), Academic Medical Center, Amsterdam, The Netherlands. [J Urol. 2015 Nov;194\(5\):1202-8](#)
- 20 patients with intermediate and high risk nonmuscle invasive bladder cancer were treated with intravesical mitomycin C (40 mg) combined with regional hyperthermia.
- The 24-month recurrence-free survival rate was 78%.

Y.H

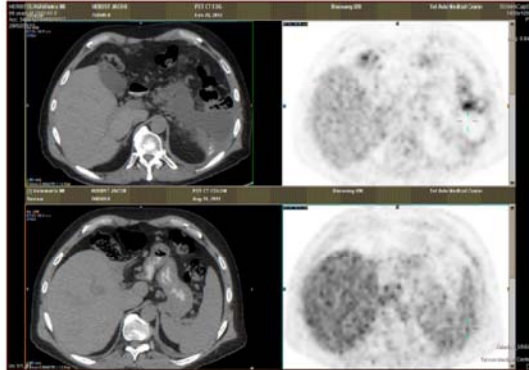
- **January 2010:** 62 Y.O with adenocarcinoma of pancreas, liver and lung metastasis. No surgery.
- Chemotherapy FOLFIRI+ Hyperthermia to abdomen and lungs, HDVC and supplements.
- **August 2012:** no metastasis in the liver and lungs. Operated to remove the pancreatic tumor: no tumor cells found.
- **2013:** died of multiple bone metastasis.

January 2010

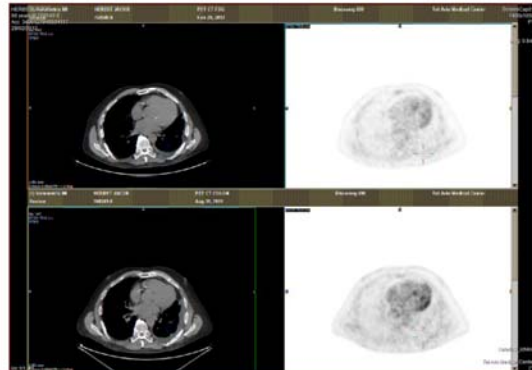


August 2012

ABDOMEN



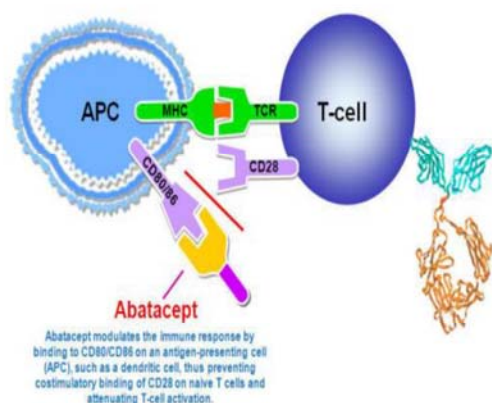
LUNGS



Hyperthermia and Hormones

- Quercetin and tamoxifen sensitize human melanoma cells to hyperthermia.
We observed that both quercetin and tamoxifen synergize with hyperthermia (42.5 degrees C)
G. D'Annunzio' University, Chieti, Italy.
Melanoma Res. 2001 Oct;11(5):469-76
- Tamoxifen and chemotherapy (CTX, DTIC or Cisplatin) enhance hyperthermia effect on melanoma cells.
Clinic of Oncology and Radiotherapy, University Hospital Center Zagreb, Zagreb, Croatia.
[Tumori](#). 2012 Mar-Apr;98(2):257-63

Hyperthermia and biologic therapy



- In this study we treated mice inoculated LLC tumors with hyperthermia or molecular target drugs (**erlotinib 25 mg/kg/day and sorafenib 10 mg/kg/day**).
- Both of hyperthermia and molecular target therapy reduced not only tumor growth but also lung metastasis.
- A combination therapy of hyperthermia and molecular target therapy reduced more of the tumor growth and lung metastasis synergistically.
- Apoptosis was enhanced by hyperthermia and molecular target drugs synergistically.

Osaka Cancer Immuno-Chemotherapy Center.
[Gan To Kagaku Ryoho](#). 2011 Nov;38(12):1924-6

Hyperthermia in combination with gefitinib in patients with advanced NSCLC

- West China School of Medicine, Sichuan University, Chengdu, China
[Thorac Cancer](#). 2016 Jul; 7(4): 422–427

- Eleven patients who responded to first-line gefitinib treatment were treat with 250 mg gefitinib daily. Local radiofrequency hyperthermia was administered twice a week until tumor progression
- Median progression-free survival was 22 months and median overall survival was 26 months
- **Hyperthermia improve and prolong the action of gefitinib.**

Cisplatin, Hyperthermia, and Lapatinib in Patients With Recurrent Carcinoma of the Uterine Cervix

• Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands
Oncologist. 2015 Mar; 20(3): 241–242.

- Eight patients with previously irradiated recurrent cervical carcinoma 6 weekly administrations of 70 mg/m² cisplatin combined with locoregional hyperthermia. Daily lapatinib was added on days 1–56.
- One CR, one PR and four SD
- The observed complete pathological response is intriguing and warrants further investigation

Supplements enhance Hyperthermia effect



- Quercetin
- Alpha Tocoferol Acetate
- Vitamin C
- Poly-Unsaturated Fatty Acids (PUFA): EPA, DHA, GLA
- K1 and K2
- Curcumin

Quarcetin and Hyperthermia

- Quarcetin enhance the reversal effect of hyperthermia on MDR when combined with chemotherapy.

Affiliated Hospital, Academy of Military Medical Sciences, Beijing, China.
[Int J Hyperthermia](#). 2008 Mar;24(2):151-9.

- Quarcetin neutralize the efficiency of Hsp70 thus it enhance the apoptotic effect of hyperthermia on cancer cells

West China Hospital, Sichuan University, Chengdu, People's Republic of China.
[Integr Cancer Ther](#). 2012 Jul 9.

Hyperthermia and EPA

- Oral EPA specifically increases the susceptibility of liver tumor tissue to lipid peroxidation, and hence enhance the antitumor effect of hyperthermia and prolongs survival.

Kyoto Prefectural University of Medicine
[Cancer Lett](#). 2002 Nov 28;185(2):139-44.

Vitamin-C and Hyperthermia

- **Enhancement of radical intensity and cytotoxic activity of ascorbate by hyperthermia.**

The combination of hyperthermia and ascorbate treatment might produce higher antitumor activity.

[Sato K, Sakagami H, Nakamura K /Japan](#)

[Anticancer Res; 16\(5A\):2987-91 1996](#)

- **Enhanced inhibitory effects of hyperthermia combined with ascorbic acid on DNA synthesis in Ehrlich ascites tumor cells grown at a low cell density.**

[Department of Radiology, Osaka City University Medical School, Japan](#)

[Cancer Biochem Biophys. 1995 Jan;14\(4\):273-80](#)

CURING HCC with HDC and Hyperthermia

- V.E: Hepato-Cellular Carcinoma
1993 HCC
- 1998 multiple hepatic and extra-hepatic metastasis
Failed all conventional treatments
Send home to die.
- Loco-Regional Hyperthermia + HDVC +supplements given intermittently for 2 years.
Complete Response= all tumors disappeared.
AFP 5000 → 20
Follow up for 8 years=NED.

At this stage, the patient was referred to Prof. Briner Josef in Tel-Aviv. She was treated there by non-conventional treatment by external heating. Detailed data are not available to us regarding the therapeutic approach and its beneficial effects. However, a dramatic response was achieved. AFP levels dropped to 27 (starting from ~ 1000) and CT studies showed shrinkage of the masses. Last CT studies showed no masses. Since then she is treated by Prof Briner with monthly maintenance injections of "VG1000". We do not have any information about these therapeutic approaches but there is a dramatic response. At this stage I recommend that our patient maintain this therapeutic modality as it is revealing a good response and although I do not have enough data despite numerous attempts to retrieve this information.

Photo Dynamic Therapy (PDT) and Hyperthermia



- Synergistic effect of photodynamic therapy with hypericin in combination with hyperthermia on loss of clonogenicity of RIF-1 cells.

Combining hypericin-mediated PDT treatment with hyperthermia could significantly enhance the cell death by necrosis as indicated by morphological examination and significant loss of membrane integrity.

- Laboratorium voor Farmaceutische Biologie en Fytofarmacologie, Faculteit Farmaceutische Wetenschappen, Katholieke Universiteit Leuven, Leuven, Belgium
Int J Oncol. 2001 Jun;18(6):1279-85

Carboplatin plus Hyperthermia and Hyperbaric Oxygen Treatment



- In animal cancer models, several studies with combined treatment of hyperbaric oxygen (HBO) and various chemotherapeutic agents have shown decrease in tumor growth.

- Department of Radiology, University of Occupational & Environmental Health, Kitakyushu, Japan
International Journal of Radiation Oncology • Biology • Physics [Volume 81, Issue 2](#), Supplement, Pages S743–S744, October 1, 2011

Paclitaxel and carboplatin plus regional hyperthermia and hyperbaric oxygen

- Twenty-two patients with NSCLC with multiple pulmonary metastases received **paclitaxel carboplatin** and **Hyperthermia (HT)** of the whole thoracic region.
16 (72%) of 22 patients received **hyperbaric oxygen (HBO)** treatment.
- Fourteen (64%) of 22 patients had an objective response. The median time to progression of disease in all patients was 8 months and in 16 patients with HBO was 9 months.
- Department of Radiology, University of Occupational and Environmental Health, Kitakyushu, Japan
[Int J Hyperthermia](#). 2009 Mar;25(2):160-7.

- ✗ 10 y/o male
- ✗ 2009 – Ependymoma diagnosis
- ✗ s/p 7 neurosurgeries
- ✗ s/p 2Xradiotherapy courses
- ✗ s/p VP-shunt d/t hydrocephelus

02/2014 – started HBOT (currently 100 sessions)

02/2014-started whole-brain Hyperthermia 2-3/week

Frontal lesion



02/2014

05/2014

07/2014

CONCLUSION

- Hyperthermia is an effective anti-cancer treatment method.
- Hyperthermia is synergistic with most other anti-cancer treatment methods and should be a part of any treatment regimen.

Workshop, local hyperthermia

Oliver Szasz*

*St. Istvan University, Department of Biotechnics, Hungary



Workshop, local hyperthermia

Oliver Szasz, PhD.

Assoc. Professor

Biotechnics Department of St. Istvan University, Hungary, &
CEO of Oncotherm Group

Outline

☐ **Decisional points**

☐ **Possible solution**

☐ **Future points**

☐ **Take-home messages**

The task

Hyperthermia is a perfect, capable method in oncology

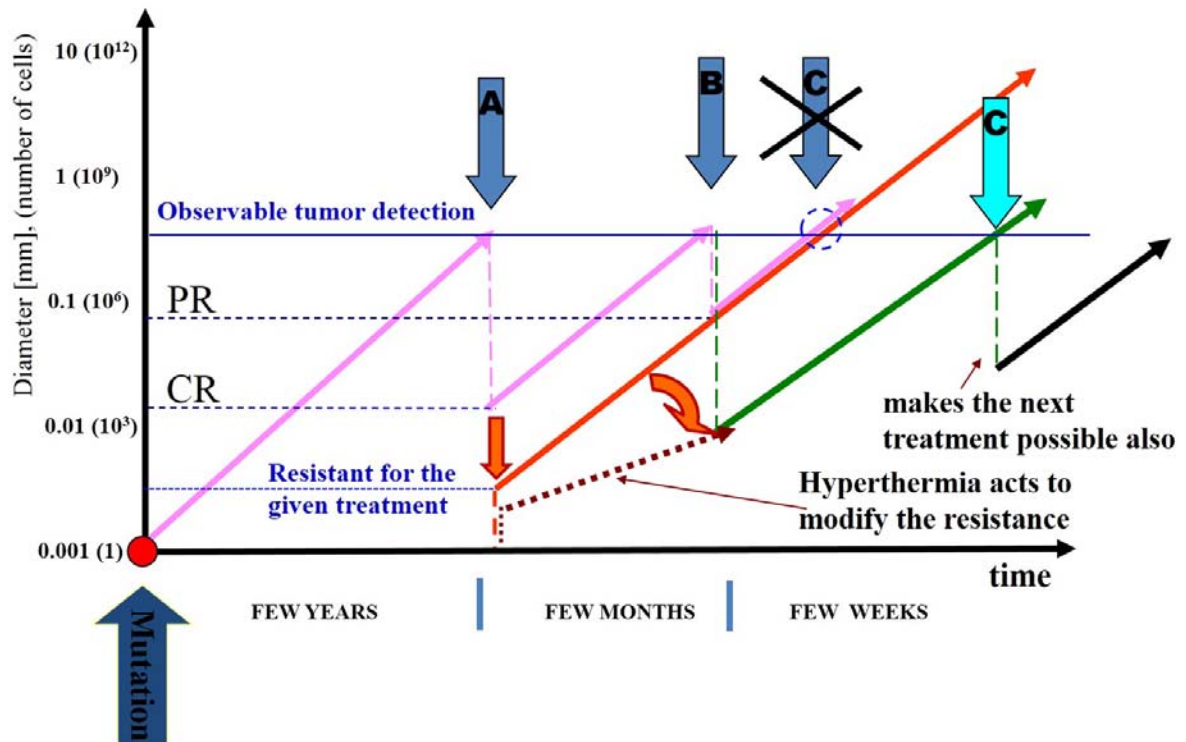
**However, we need further development
and think about the decisional points**

The task

Decisional point 1

**Development of tumor resistance
against chemo-therapy**

Development of tumor resistance against chemotherapy

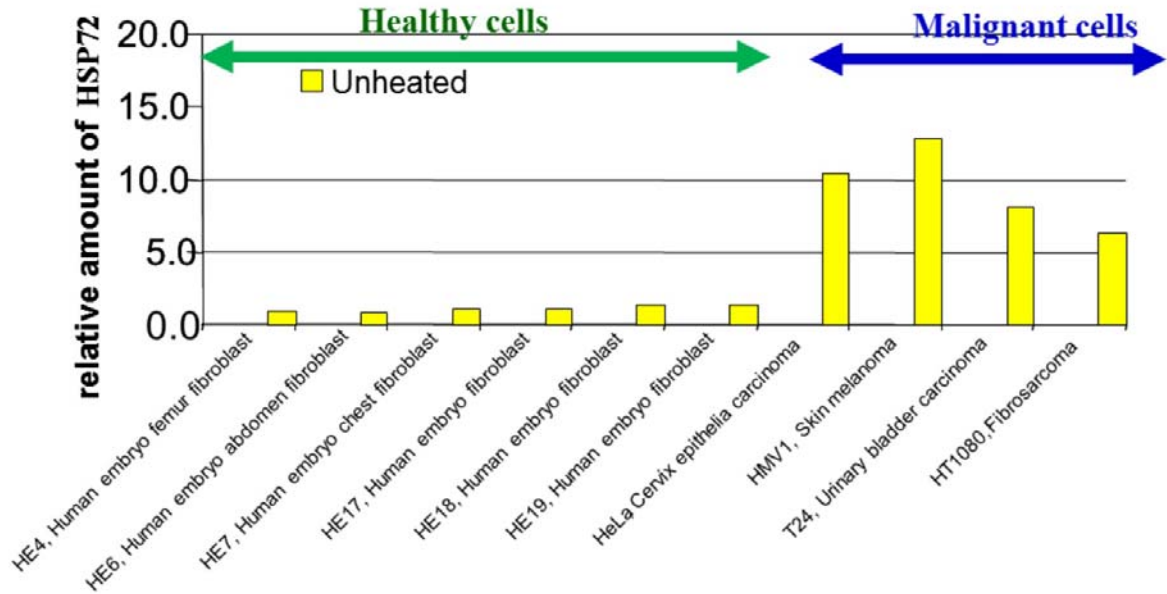


The task

Decisional point 2

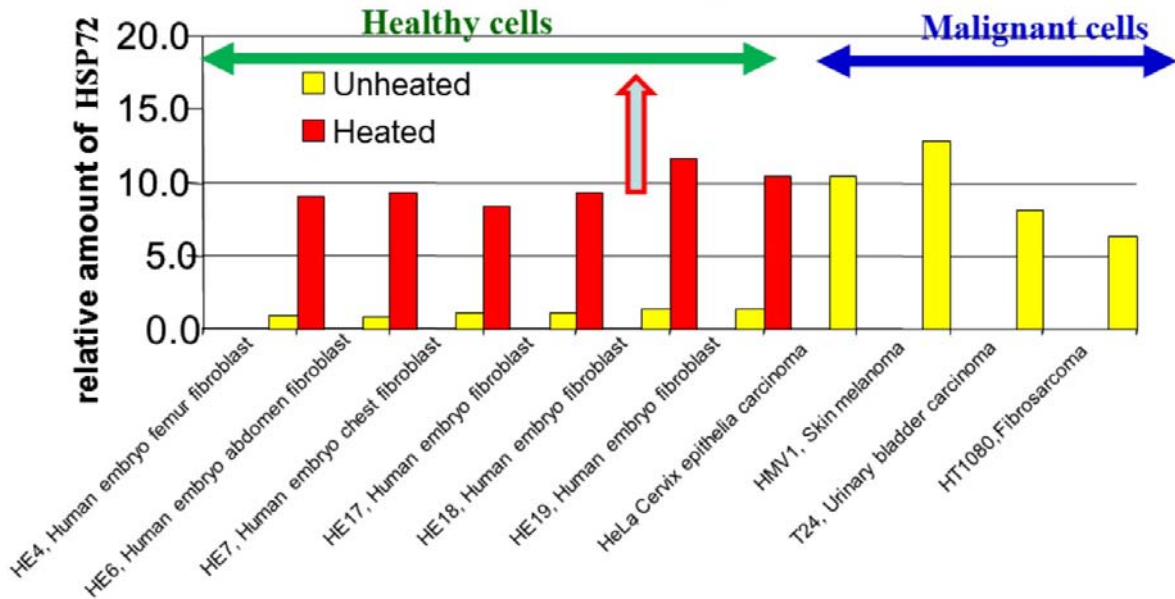
Selective protection

Relative sensitivity of malignant cells

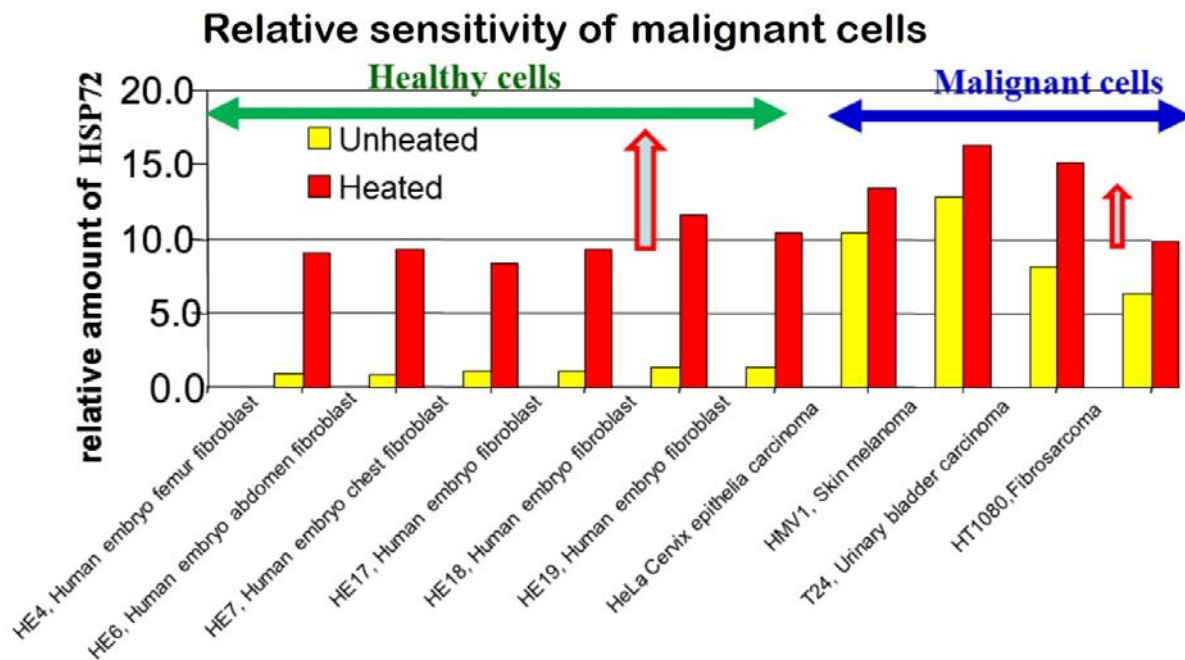


M. Watanabe et al.: Normal human cells at confluence get heat...
Carcinogenesis vol. 16. no. 10 pp. 2373-2380, 1995

Relative sensitivity of malignant cells



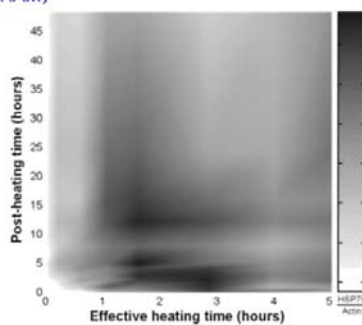
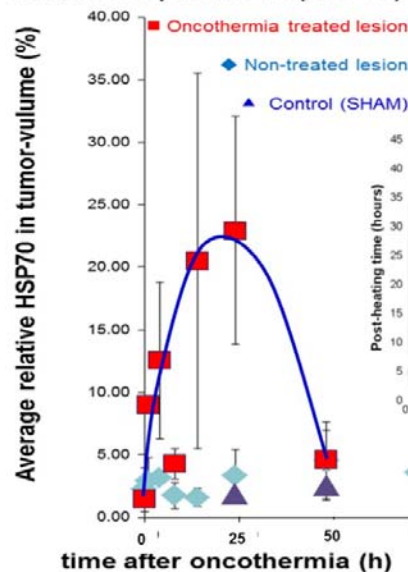
M. Watanabe et al.: Normal human cells at confluence get heat...
Carcinogenesis vol. 16. no. 10 pp. 2373-2380, 1995



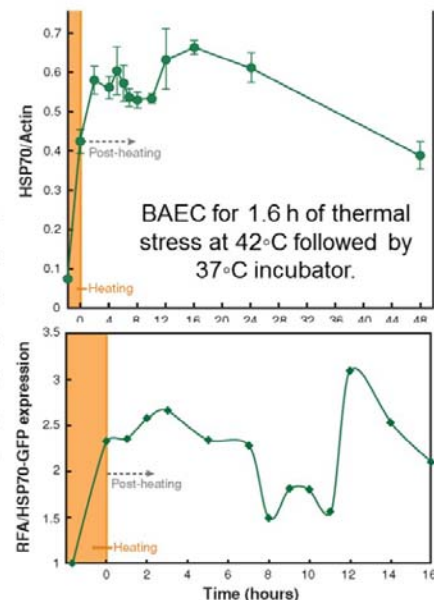
M. Watanabe et al.: Normal human cells at confluence get heat...
 Carcinogenesis vol. 16. no. 10 pp. 2373-2380. 1995

Relative sensitivity of malignant cells

Heat shock protein 70 (HSP70)



BAEC for thermal stress at 42°C followed by the indicated recovery periods in a 37°C incubator
 BAEC - bovine aortic endothelial cell
 HSP27
 Diller KR (2006) Annu. Rev. Biomed. Eng. 8:403-424



Diller KR (2006) Annu. Rev. Biomed. Eng. 8:403-424

The task

Decisional point 3

The threshold challenge

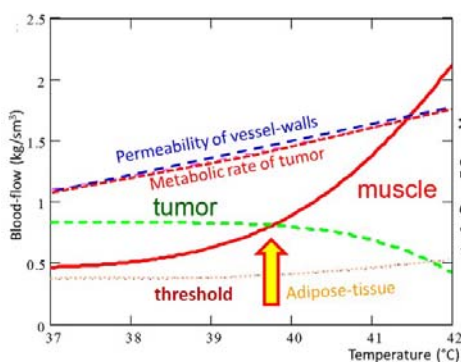
Threshold challenges

Hyperthermia is mostly complementary treatment

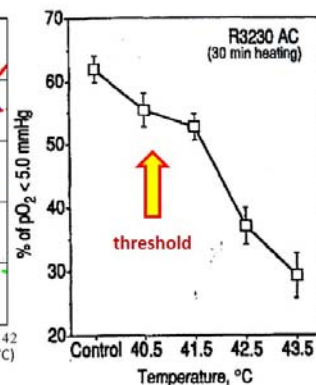
- Chemotherapy needs high blood-flow to deliver the drug
- Radiotherapy needs high blood-flow for proper oxygen content
- Immuno-simulation needs higher blood-flow and fever

Hyperthermia sensitizes all the “gold-standards”, it looks perfect sensitizer

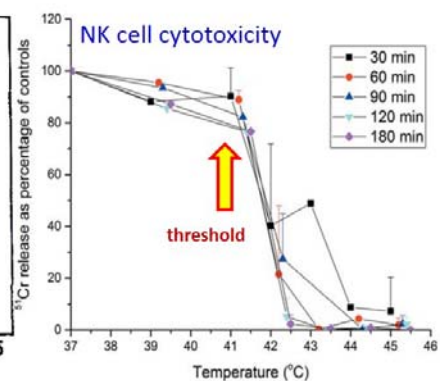
However, as usually, the overdosing of the therapy turns the usefulness



Erdmann B., Lang J. Seebass M.: Optimization of temperature distributions for regional hyperthermia based on a nonlinear heat transfer model, Annals of NYAS, 858, 36-46, September 1998



Song CW et.al: (2009) Tumor oxygenation is increased by hyperthermia at mild temperatures, Int.J. Hyperthermia, 25:91-95

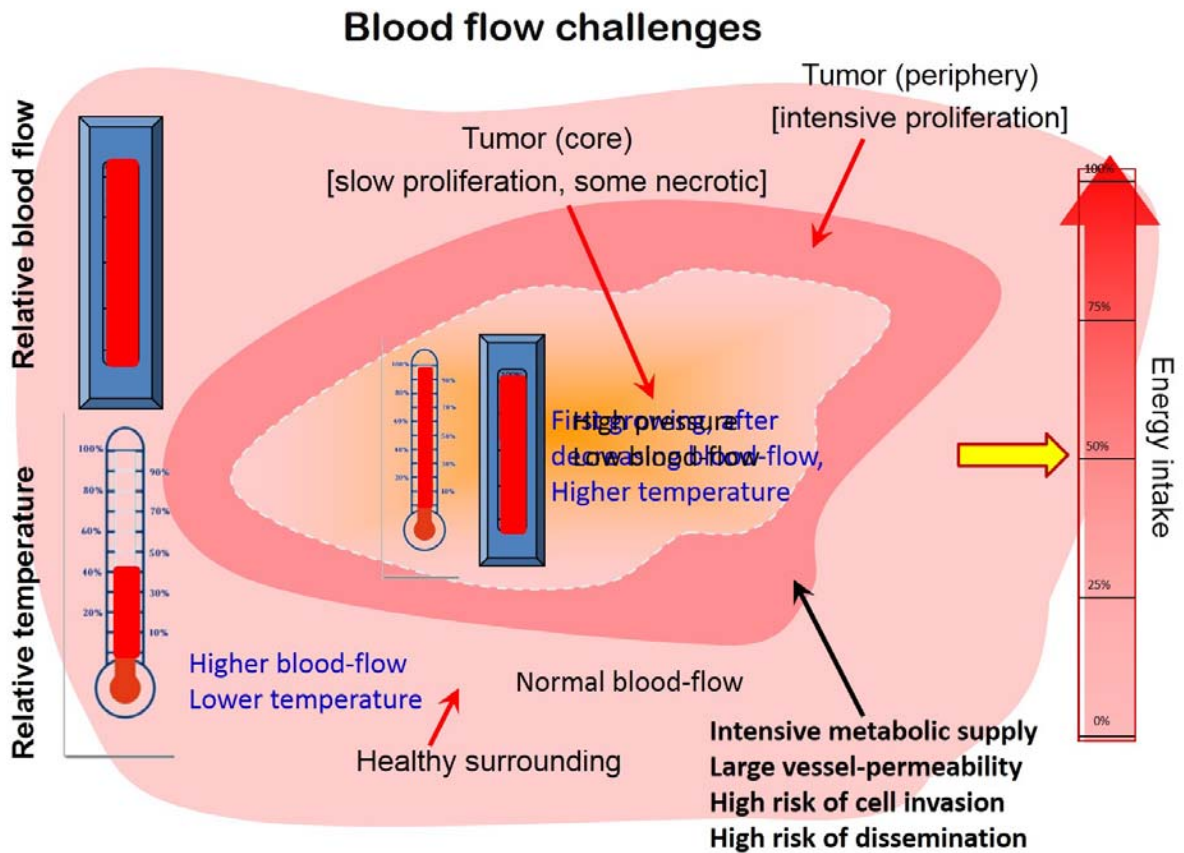


Hietanen T et al. Restoring Natural Killer Cell Cytotoxicity After Hyperthermia Alone or Combined with Radiotherapy, ANTICANCER RESEARCH 36: 555-564 (2016)

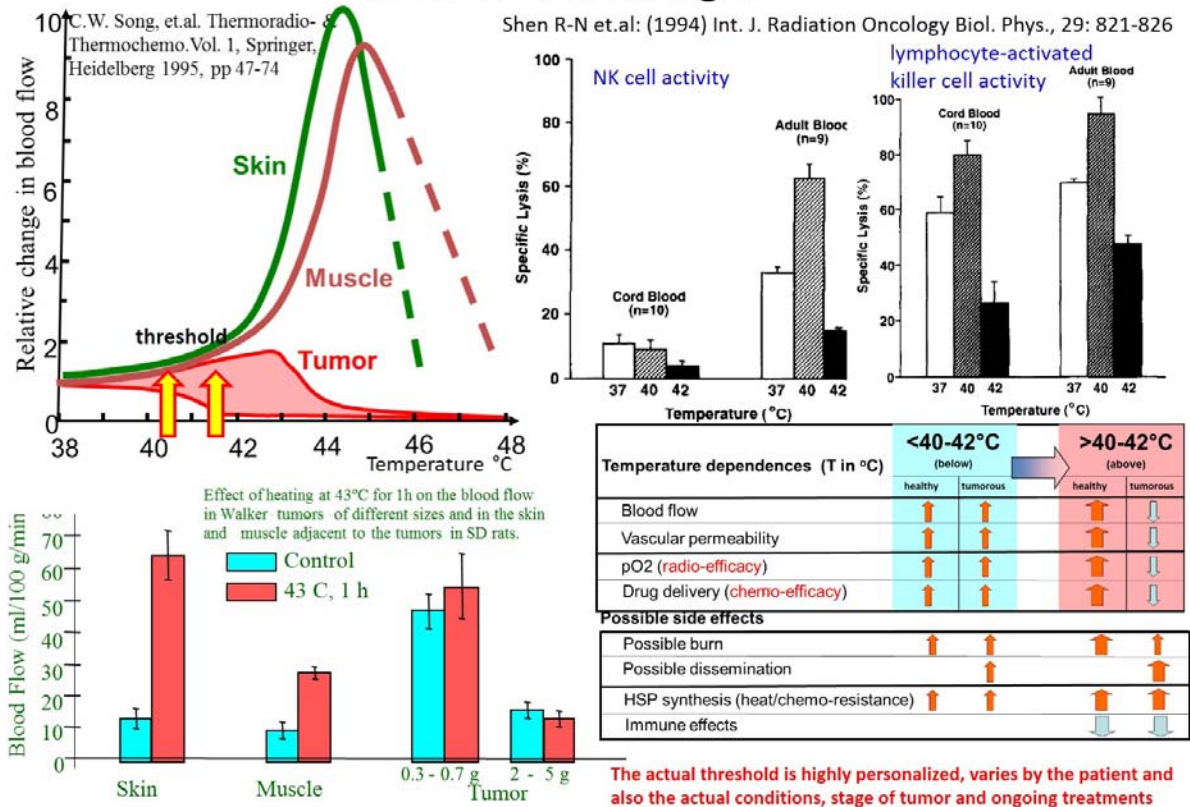
The task

Decisional point 4

The blood-flow challenge



Blood flow challenges

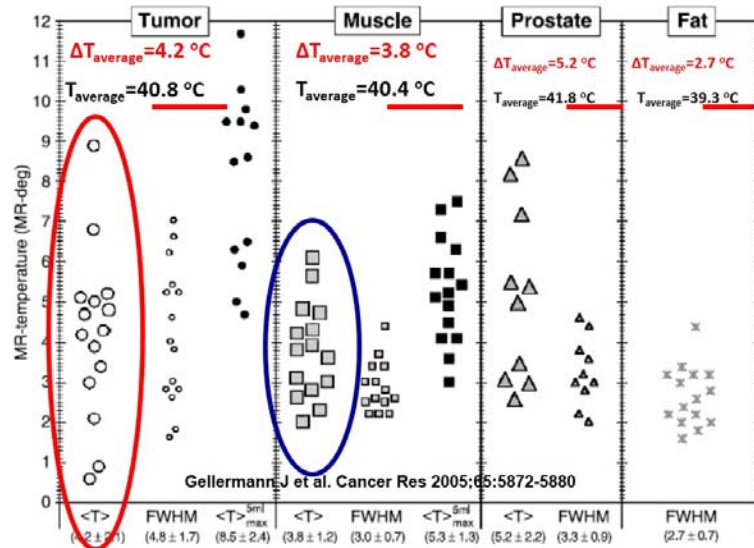


The task

Decisional point 5

The heterogeneity challenge

Heterogeneity of temperature

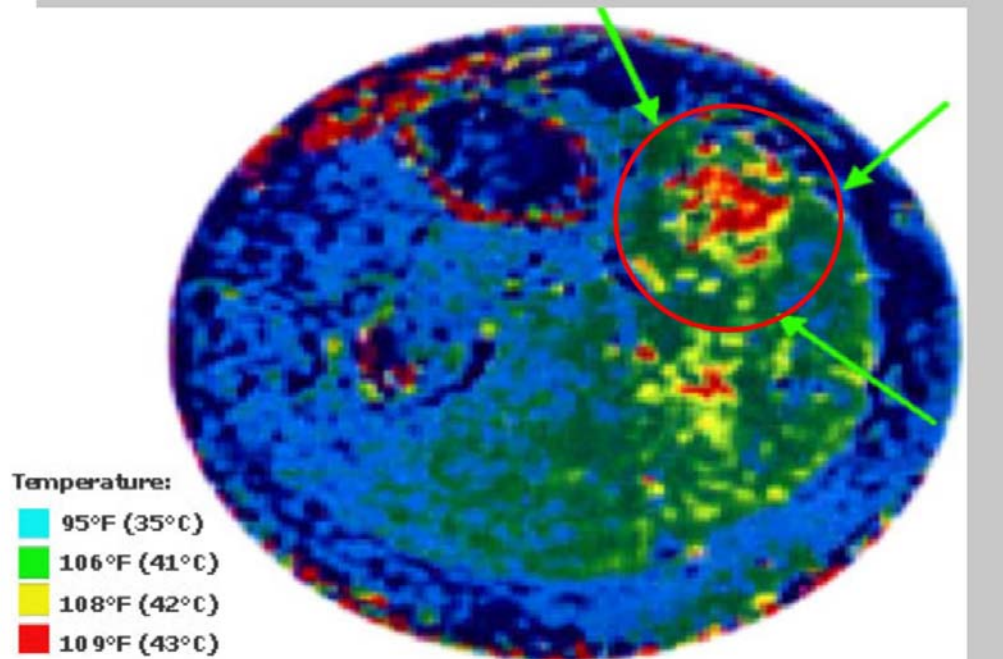


The task

Decisional point 6

The focusing challenge

Focusing



Example of non-invasive temperature measurements made during treatment in a patient with a soft tissue sarcoma of the lower leg (arrows). The colors indicate the temperatures reached during this part of the treatment, which range from 95-109°F (35-42.7°C).

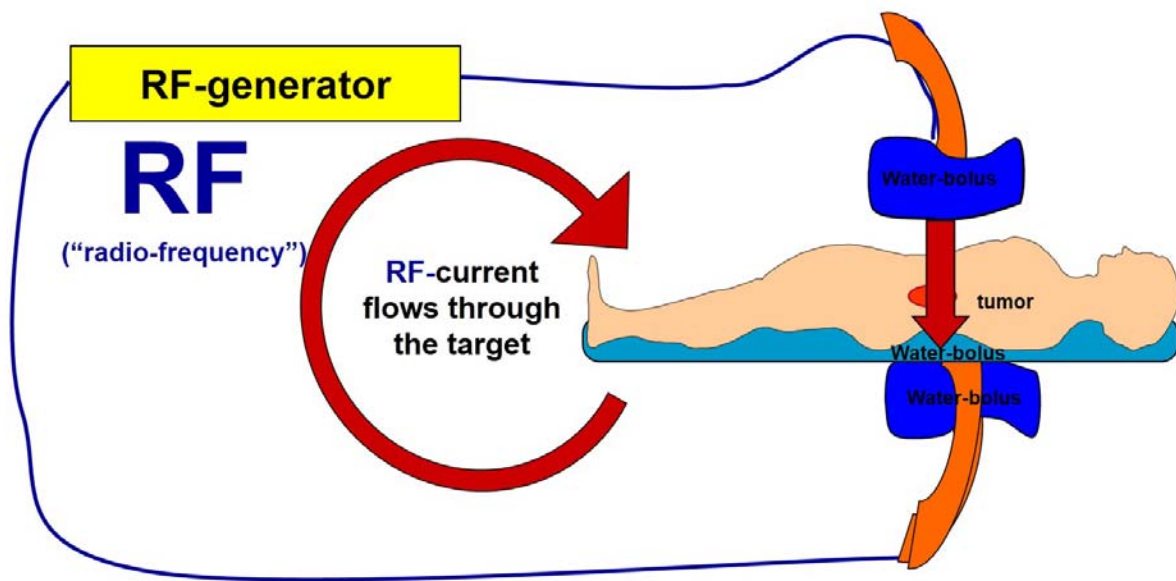
http://hyperthermia.mc.duke.edu/sp_research.htm

The task

Decisional point 7

The matching challenge

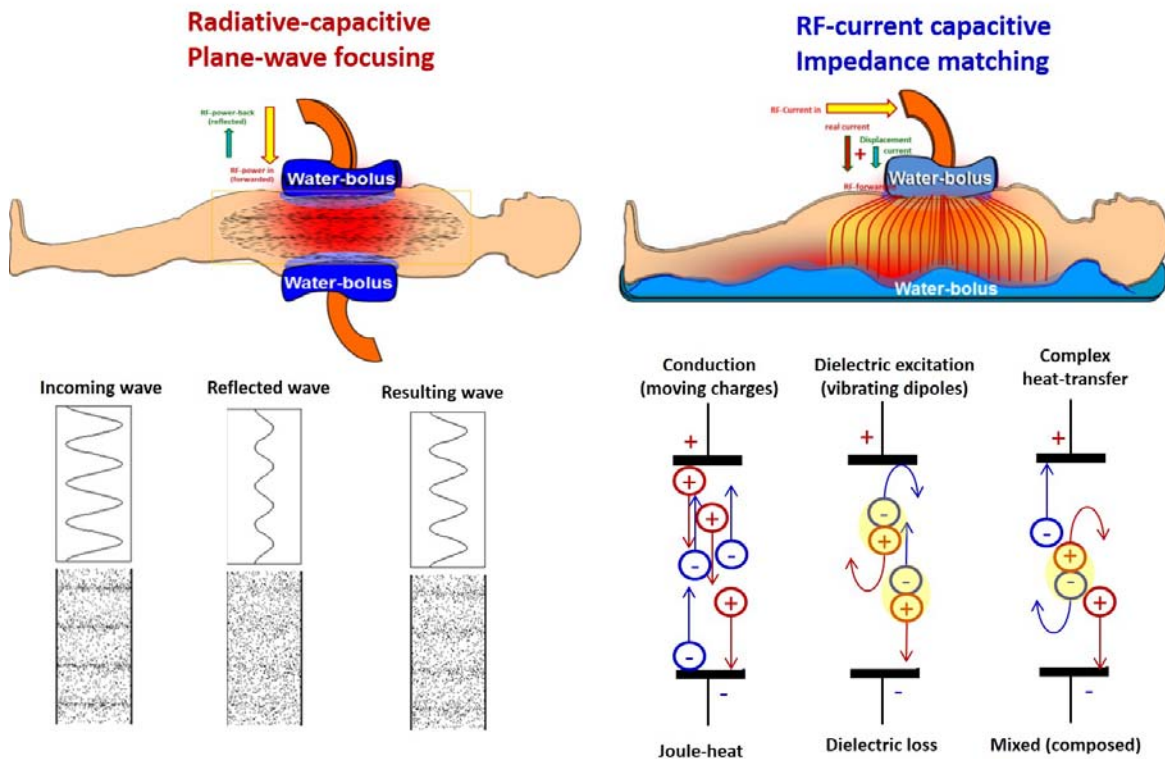
Type of treatment



Energy is carried by RF-current, targeting the absorbers

Patient is a part of the RF electric circuit

Principles of capacitive electric targeting



The task

Decisional point 8

Targeting (safety) challenge

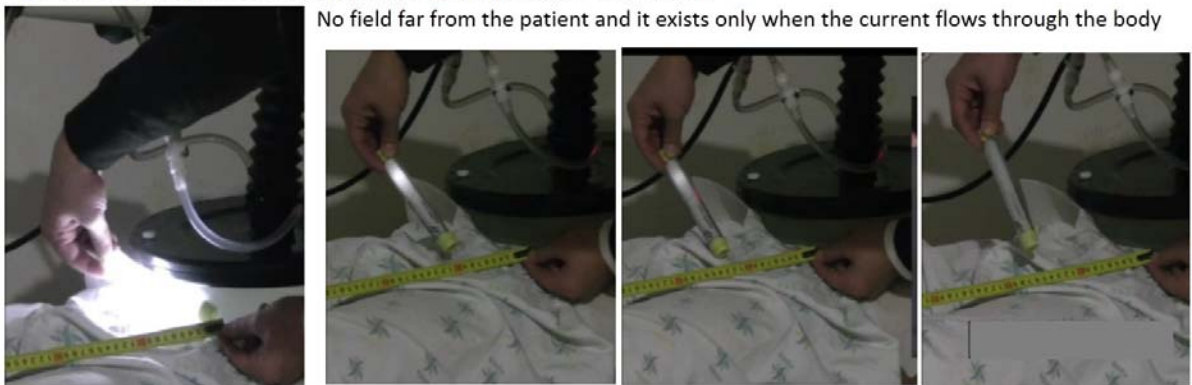
Differences between the capacitive couplings

Radiative capacitive coupling: long distance radiation, even without patient



RF-current capacitive coupling: short distance radiation

No field far from the patient and it exists only when the current flows through the body



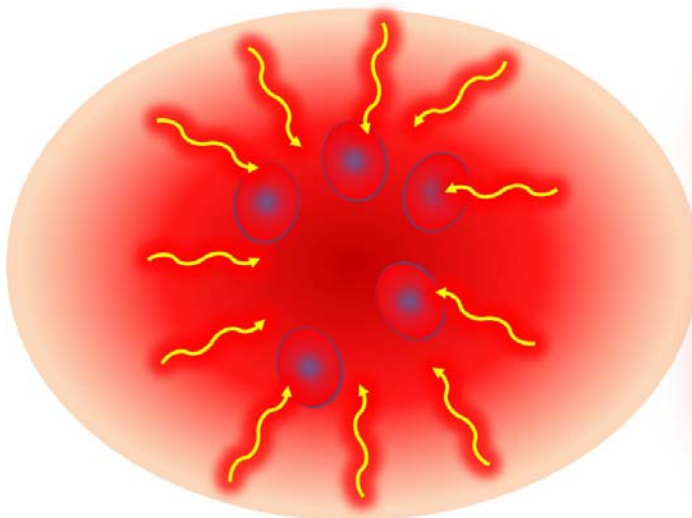
The task

Decisional point 9

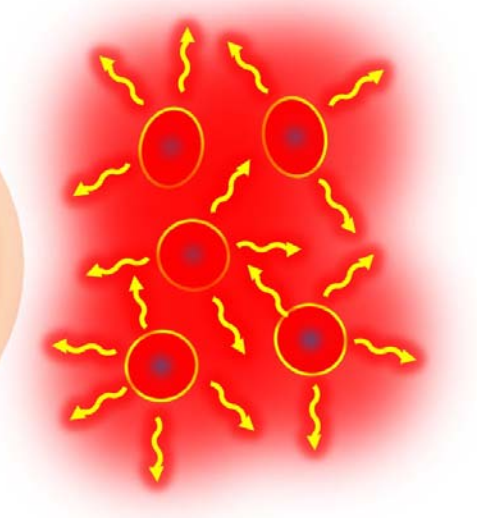
The heat-flow challenge

Concept of homogenic and heterogenic heating

Conventional homogeneous heating
(radiation + conduction + convection)



Selective heterogeneous heating
(targeting tissues, groups of molecules, etc.)

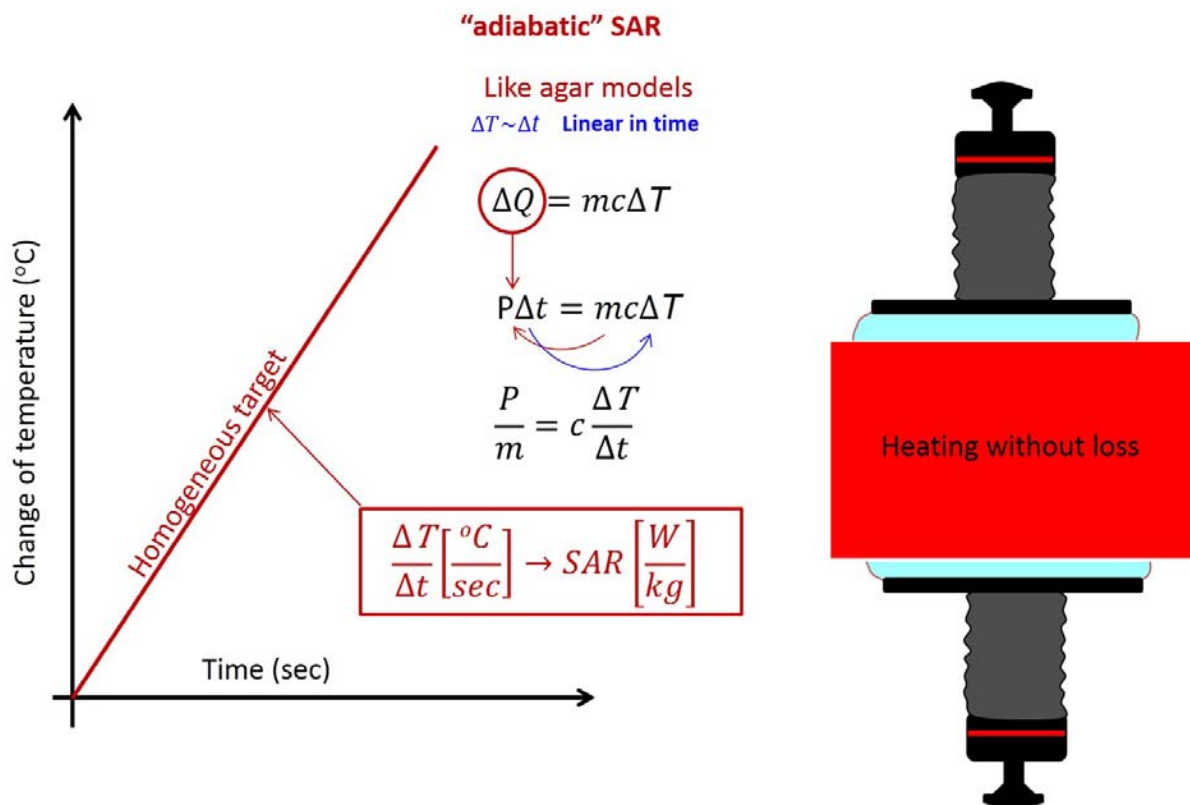


The task

Decisional point 10

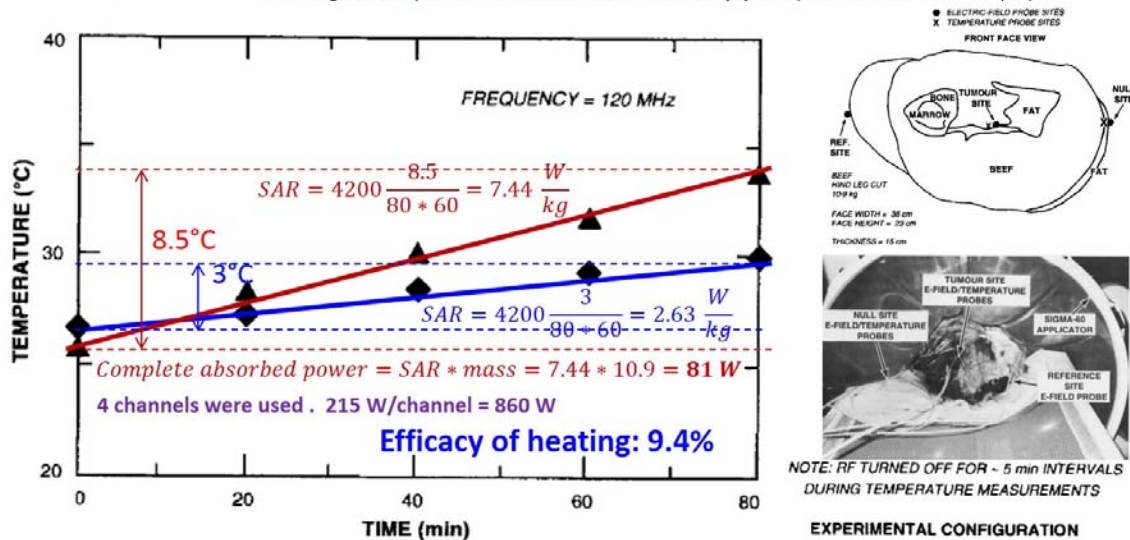
The dosing challenge

Challenge of targets



Challenge of unknown losses: BSD2000

Temperature Measured temperatures in the beef phantom. Eighty minutes after the start of the experiment. a 4°C higher temperature exists at the tumor site (Δ) compared to the null site (◆).



The beef phantom used in these experiments is a tapered cut obtained from the hind leg just above the knee. The front face of the beef has a horizontal width of 38 cm and a vertical height of 23 cm. The thickness of the beef is 15 cm and the weight is 10.9 kg.

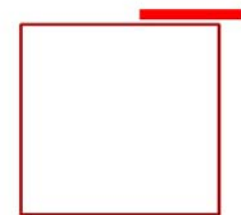
Fenn AJ, King GA. Adaptive radiofrequency hyperthermia-phased array system for improved cancer therapy: phantom target measurements. Int. J. Hyperthermia. 10:189-208 (1994)

Challenge of the unknown losses: Thermotron

Agar gel mass density is $0.999 \pm 0.004\ kg/liter$

Liliana Aranda-Lara, Eugenio Torres-García, Rigoberto Oros-Pantoja. Biological Tissue Modeling with Agar Gel Phantom for Radiation Dosimetry of ^{99m}Tc . Open Journal of Radiology. 2014. 4. 44-52

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



$$M = \frac{\pi h \rho}{3} (r^2 + R^2 + rR)$$

$$M \approx 1.4\ kg$$

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

$$SAR = 70 \frac{W}{kg}$$

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

$$SAR = 40 \frac{W}{kg}$$

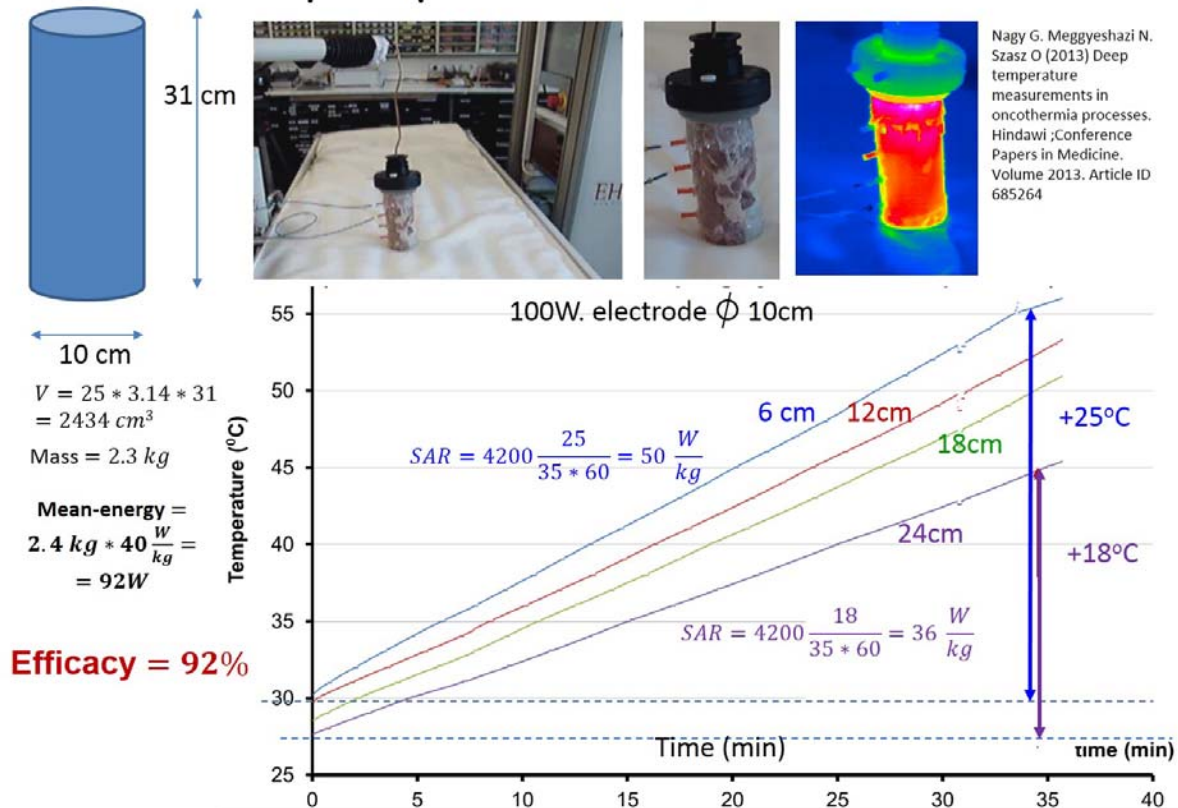
$$SAR = 35 \frac{W}{kg}$$

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

700 W was used, efficacy is 14%

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 (1986)

Deep-temperature measurements



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

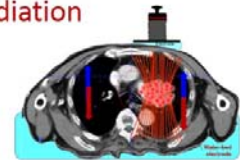
Dose for thermal effect

The normal dose of thermal effect depends on the energy absorption of the target.

When the absorption efficacy is low (like BSD < 10%. Thermotron < 15%) then the only way to measure the absorbed energy is the temperature because the forwarded power veer weekly depends on the useful energy absorption.



When the absorption efficacy is high (like oncothermia > 90%) then the classical measurement of the absorbed energy is the dose like in the ionizing radiation therapies.



Open Journal of Biophysics, 2015, 5, 97-114
Published Online October 2015 in SciRes. <http://www.scirp.org/journal/ojbiophy>
<http://dx.doi.org/10.4236/ojbiophy.2015.54009>

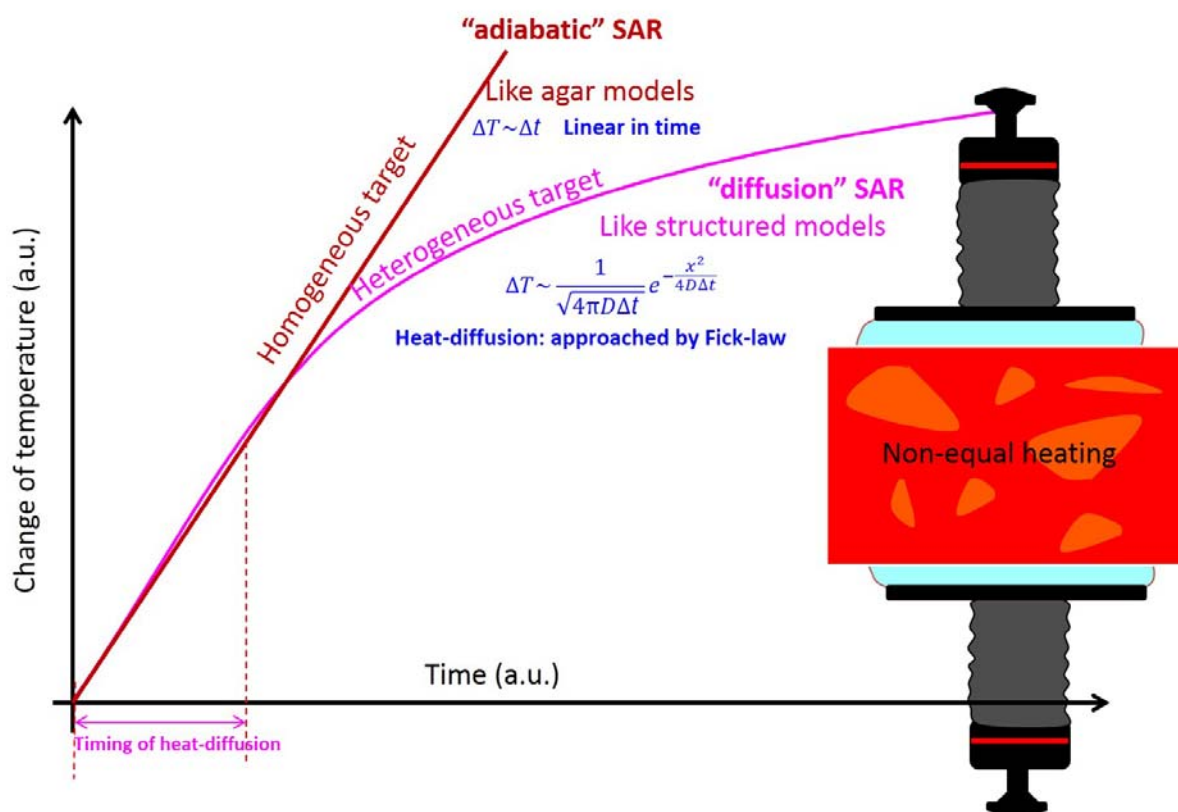


Generalization of the Thermal Dose of Hyperthermia in Oncology

Gyula Vincze, Oliver Szasz, Andras Szasz*

Szent István University, Gödöllő, Hungary
Email: Szasz.Andras@gek.szie.hu

Challenge of targets

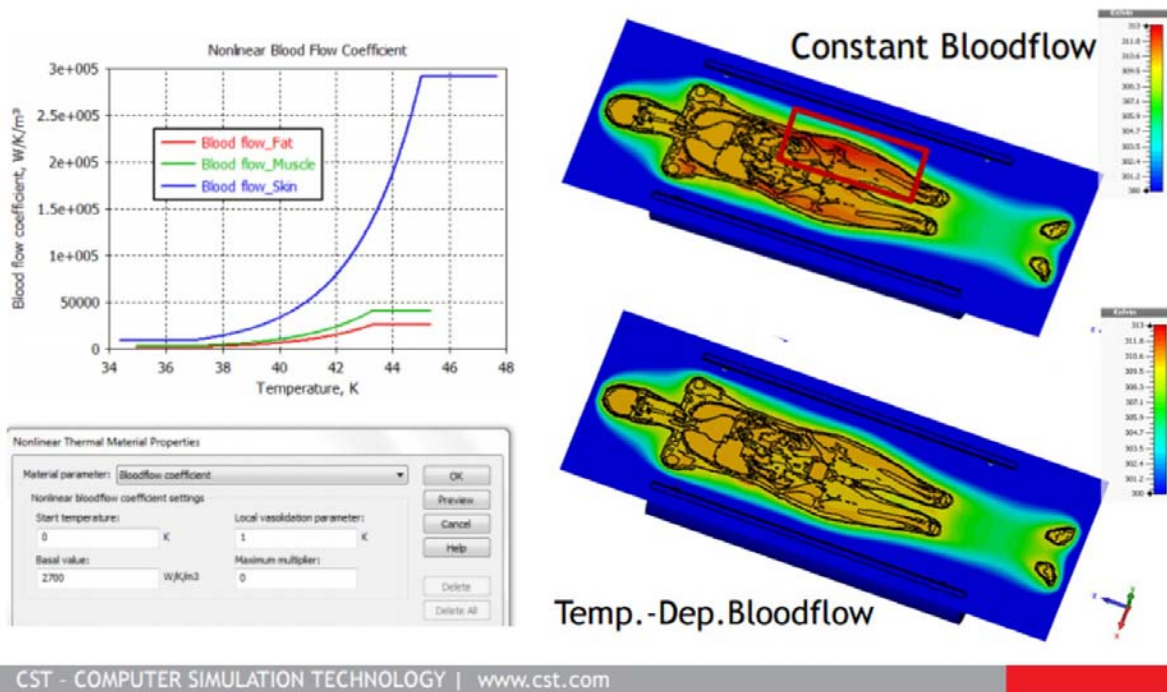


The task

Decisional point 11

The physio-feedback challenge

Challenge of the model-construction



CST - COMPUTER SIMULATION TECHNOLOGY | www.cst.com

<https://www.cst.com/Content/Events/Downloads/euc2014/4.2.3.pdf>

The task

Decisional point 12

The principle challenge and its consequences

Comparison of the basic principles, the mechanism of action, the technical realization and its biological effects of Thermotron and Oncothermia method

RF-hyperthermia
Thermotron RF-8

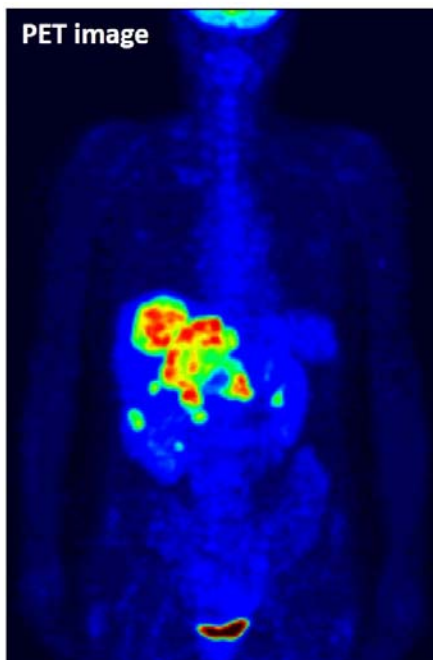
Vs.

Oncothermia
EHY-2000



The similarity

Both methods take advantage on the same principle:
Tumor tissue has higher RF absorption than the healthy tissue



Malignant tissue has much higher glucose influx and higher metabolic rate than healthy tissue (FDG-PET is based on this phenomenon)



Increased concentration of metabolites in the extracellular electrolyte in the malignant tissue



High ionic concentration



High electrical conductivity

The higher electrical conductivity can be directly measured!

INSTITUTE OF PHYSICS PUBLISHING
Physiol. Meas., 24 (2003) 251–260

PHYSIOLOGICAL MEASUREMENT
PII: S0967-3334(03)56535-2

Technology in Cancer Research and Treatment
ISSN 1533-0346
Volume 5, Number 4, August (2006)
©Adenine Press (2006)

In vivo electrical conductivity of hepatic tumours

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D Haemmerich *et al*

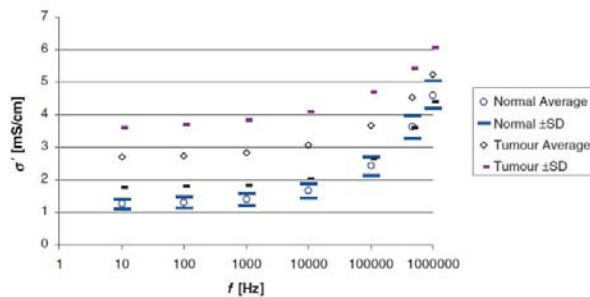


Figure 4. Mean $\pm$ SD. Electrical conductivity of tumour and normal liver tissue.

In Vivo MRI Electrical Impedance Tomography (MREIT) of Tumors

www.tctt.org

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Mark J. Hamamura, Ph.D.
Ozlem Birgul, Ph.D.
Orhan Nalcioğlu, Ph.D.

John Tu & Thomas Yuen Center for
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164 Irvine Hall
Irvine, CA 92697-5020, USA

A significant increase in electrical conductivity of neoplastic tissues compared to healthy tissues and benign formations has been reported in several studies. We previously reported preliminary results with MR based Electrical Impedance Tomography (MREIT) on several phantoms and a single animal. In the presented study, we applied the technique on ten tumor-bearing rats and collected MREIT images to investigate the potential of MREIT for characterizing malignant tumors. Results show that the tumors had significantly higher mean conductivity compared to the mean of conductivity in the rest of the body. Although heterogeneity of conductivity was observed in the tumor, the mean was still higher than the background.

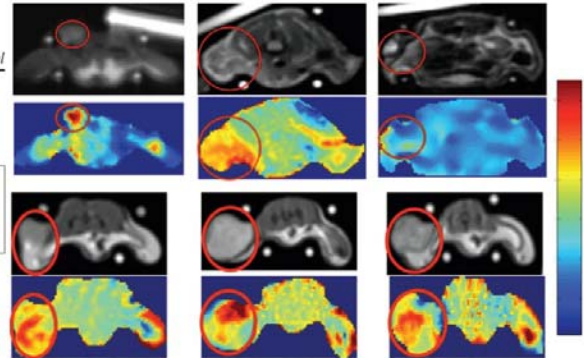


Figure 4: Structural and MREIT images of six animals are illustrated. Anatomic (T2 weighted) scans are displayed in gray levels and corresponding impedance (MREIT) images are depicted in color right below the T2 weighted images. Each image pair shows axial images from different animals. Tumor areas are circled with red lines. Bright objects outside the animals' body were markers to identify exact location of electrodes.

The difference : basic principle in tumor cell destruction

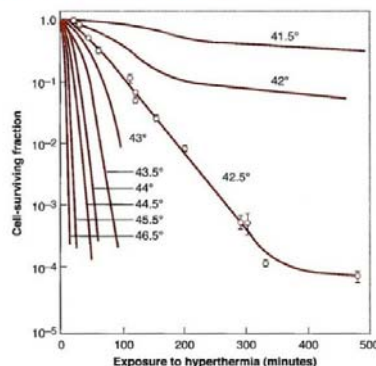


RF-hyperthermia
Thermotron RF-8

Classic hyperthermia concept:

Reach the cytotoxic level temperature range ($>43^{\circ}\text{C}$) quickly and keep the tumor on this temperature range as necessary

Homogenous, equilibrium heating – the **tumor temperature is very important**

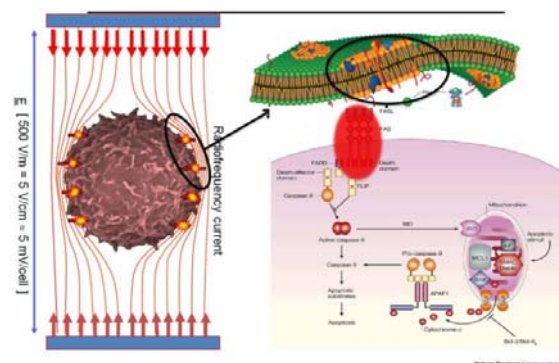


Oncothermia
EHY-2000

New hyperthermia concept:

Keep the tumor temperature below the cytotoxic range ($<42^{\circ}\text{C}$) but induce continuous temperature gradient on the tumor cell membrane

Inhomogenous, non-equilibrium heating – the **temperature gradient is important**



Consequences of the different basic principles



RF-hyperthermia
Thermotron RF-8

Classic hyperthermia concept:

Homogenous, equilibrium heating at cytotoxic temperature range



Necrotic cancer cell death, the tumor destruction rate is highly temperature dependent



Significant protein denaturation, tumor antigens also destroyed



Inflammation



Limited possibility for immunotherapy combinations



Oncothermia
EHY-2000

New hyperthermia concept:

Inhomogenous, non-equilibrium heating below cytotoxic temperature range



Temperature gradient on the membrane induce signal transduction pathways resulting programmed cancer cell death



No protein denaturation occur, tumor antigens became recognizable, DAMP is generated



Immunogenic cancer cell death



Good basis for immunotherapy combinations

Experimental proofs of the new hyperthermia concept

Tsang et al. *BMC Cancer* (2015) 15:708
DOI 10.1186/s12885-015-1690-2



RESEARCH ARTICLE

Open Access



Improving immunological tumor microenvironment using electro-hyperthermia followed by dendritic cell immunotherapy

Yuk-Wah Tsang^{1,2}, Cheng-Chung Huang³, Kai-Lin Yang³, Mau-Shin Chi³, Hsin-Chien Chiang³, Yu-Shan Wang³, Gabor Andocs⁴, Andras Szasz⁴, Wen-Tyng Li^{5*} and Kwan-Hwa Chi^{3,6*}

Abstract

Background: The treatment of intratumoral dendritic cells (DCs) commonly fails because it cannot evoke immunity in a poor tumor microenvironment (TME). Modulated electro-hyperthermia (mEHT, trade-name: oncothermia) represents a significant technological advancement in the hyperthermia field, allowing the autofocusing of electromagnetic power on a cell membrane to generate massive apoptosis. This approach turns local immunogenic cancer cell death (apoptosis) into a systemic anti-tumor immune response and may be implemented by treatment with intratumoral DCs.

Methods: The CT26 murine colorectal cancer model was used in this investigation. The inhibition of growth of the tumor and the systemic anti-tumor immune response were measured. The tumor was heated to a core temperature of 42 °C for 30 min. The matured synergetic DCs were intratumorally injected 24 h following mEHT was applied.

Results: mEHT induced significant apoptosis and enhanced the release of heat shock protein70 (Hsp70) in CT26 tumors. Treatment with mEHT-DCs significantly inhibited CT26 tumor growth, relative to DCs alone or mEHT alone. The secondary tumor protection effect upon rechallenging was observed in mice that were treated with mEHT-DCs. Immunohistochemical staining of CD45 and F4/80 revealed that mEHT-DC treatment increased the number of leukocytes and macrophages. Most interestingly, mEHT also induced infiltrations of eosinophil, which has recently been reported to be an orchestrator of a specific T cell response. Cytotoxic T cell assay and ELISpot assay revealed a tumor-specific T cell activity.

Conclusions: This study demonstrated that mEHT induces tumor cell apoptosis and enhances the release of Hsp70 from heated tumor cells, unlike conventional hyperthermia. mEHT can create a favorable tumor microenvironment for an immunological chain reaction that improves the success rate of intratumoral DC immunotherapy.

Keywords: Dendritic cells, Modulated electro-hyperthermia, Immunotherapy, Tumor microenvironment

and the promotion of immunogenic signals in a colorectal cancer model using electro-hyperthermia

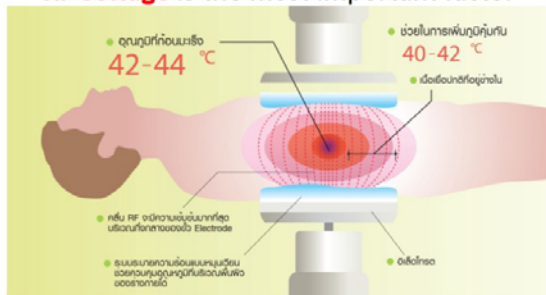
Immunogenic cancer cell death response upon mEHT treatment accompanied by the early upregulation (4-h post-treatment) of heat shock protein (Hsp70 and Hsp90) levels. In situ, the treatment resulted in spatial occurrence of a DAMP protein signal sequence induced by the significant cytoplasmic to cell membrane translocation of calreticulin at 4 h, Hsp70 between 14 h and Hsp90 between 24- and 216-h post-treatment. The release of high-mobility group box 1 protein (HMGB1) from tumor cell nuclei from 24-h post-treatment and its clearance from tumor cells by 48 h was also detected. Our results suggest that mEHT treatment can induce a DAMP-related signal sequence in



RF-hyperthermia
Thermotron RF-8

capacitive planewave coupling

RF voltage is the most important factor



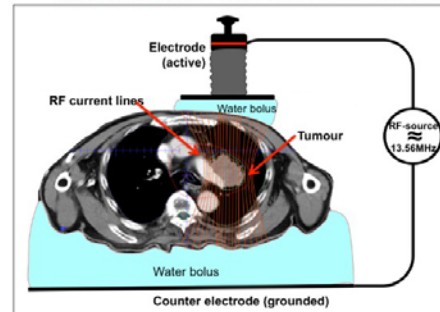
The electrodes in this case like antennas are sources of RF waves. Air layers or bubbles can not block the wave propagation in this concept.



Oncothermia
EHY-2000

capacitive impedance coupling

RF-current is the effective factor



In capacitive impedance coupling the applicators are real electrodes that need as tight connection to the target as possible, because the RF-current must flow through the target that makes the effect. The impedance is the treated body, and the biological effect is expected from the current-flow through it, so no air or unproven isolation could be applied.

II. Applied power and electrode cooling



RF-hyperthermia
Thermotron RF-8

Relatively weak coupling + necessity of high temperature range to reach the cytotoxic level

1500 W

The very high RF power needs extreme surface cooling to prevent the skin burn



The cooling water temperature is around +4 °C



Skin surface temperature is below the physiological range



Oncothermia
EHY-2000

Strong impedance coupling + mild hyperthermia range

150 W

The low RF power needs only moderate cooling



The cooling water temperature is around +25 °C



Skin surface temperature is in the physiological range



RF-hyperthermia
Thermotron RF-8

III. Electrode configuration



Oncothermia
EHY-2000

Double symmetric electrode configuration:

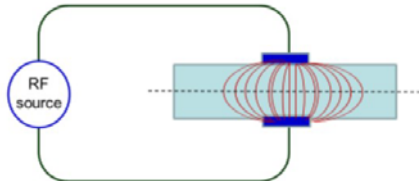
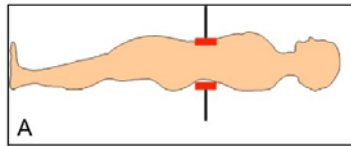
In geometry: two equal size and shape electrodes

In electronics: both electrodes are equal

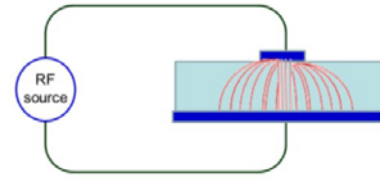
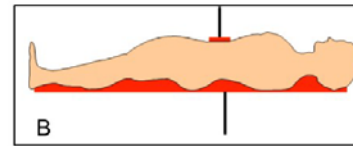
Double asymmetric electrode configuration:

In geometry: one large and one small electrode

In electronics: the large electrode is directly grounded (reference point), the smaller electrode is the active electrode



RF-hyperthermia
Thermotron RF-8



Oncothermia
EHY-2000

IV. Operation frequency

8 MHz



Not a free frequency



Can not be used freely



The operation of the RF-8 system needs a special, very expensive RF shielded room

13.56 MHz



ISM band - free frequency



Can be used without a limitation



The EHY-2000 device can be operated anywhere without a shielded room

Are these challenges real?

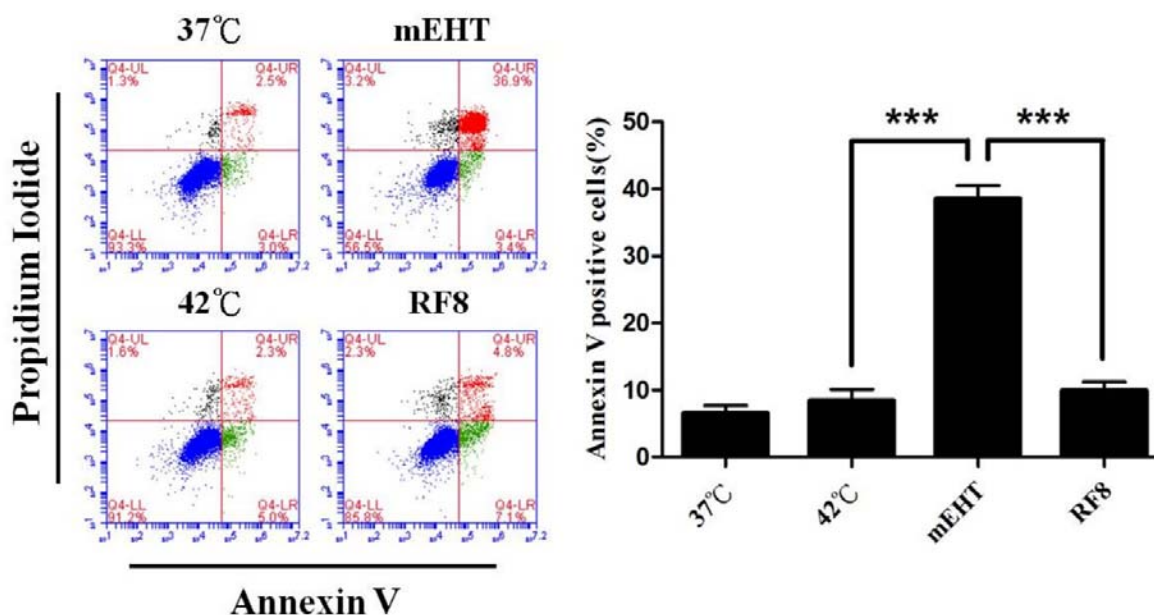
**Different basic principles of operation result
different technical solutions in the device!**

Experimental comparison of the induced
biological effect of RF-8 and mEHT



Dr. Wang et al.
Taiwan National Univ.

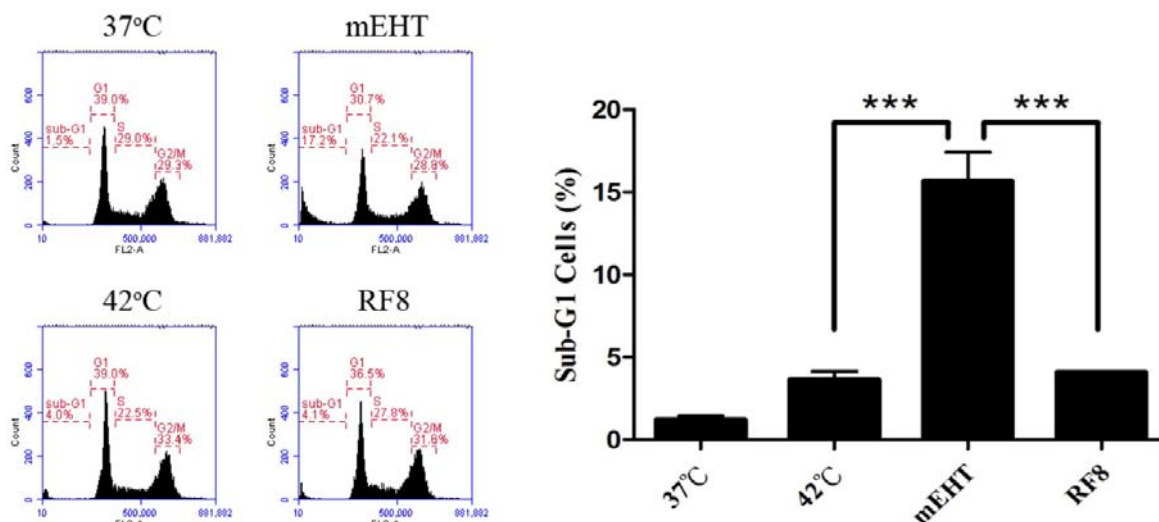
Results





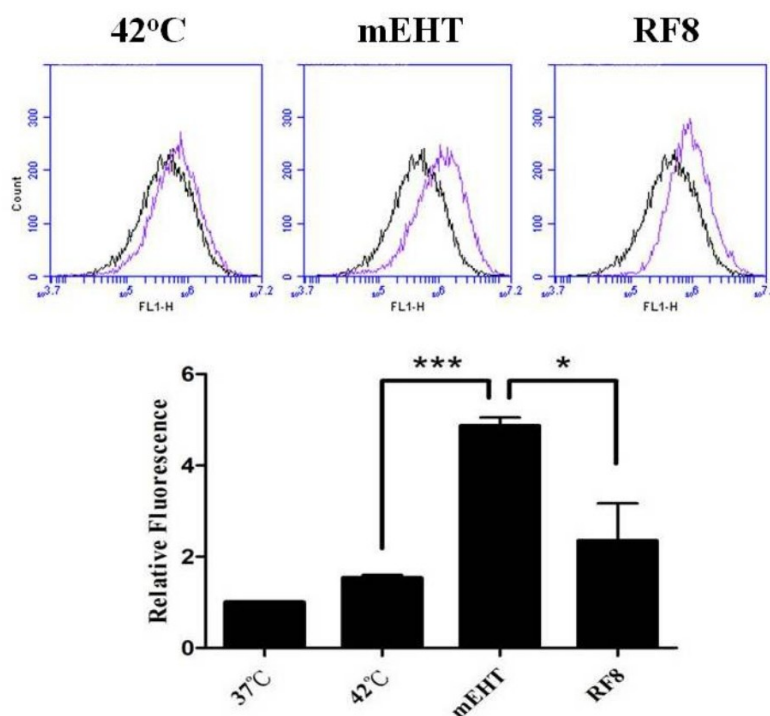
Results

Cell death analysis: Cell cycle distribution analysis



Results

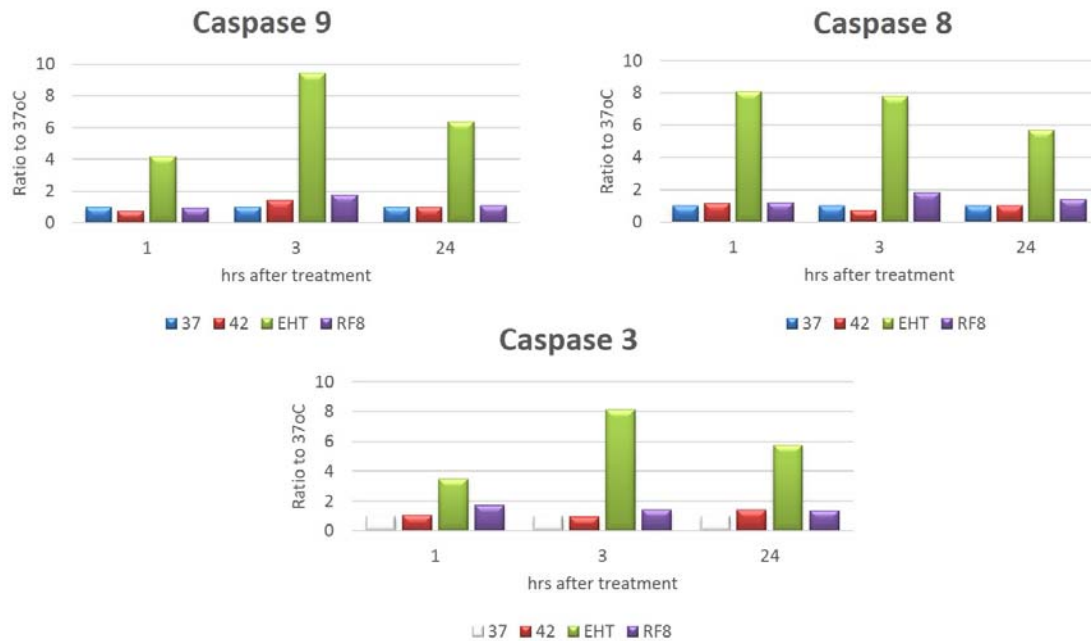
Cell death analysis: Total cellular ROS level





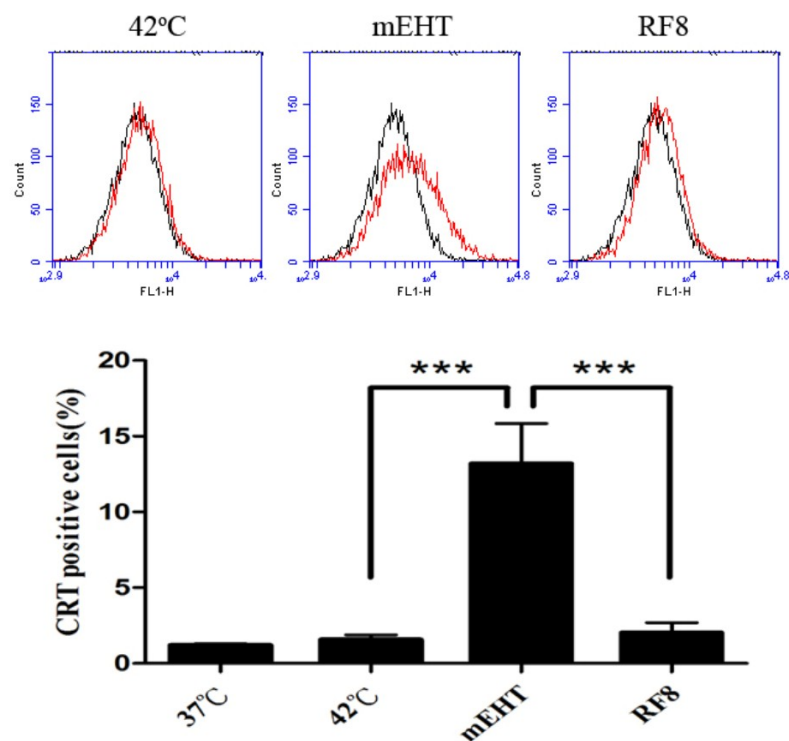
Results

Cell death analysis: The caspase signaling pathway



Results

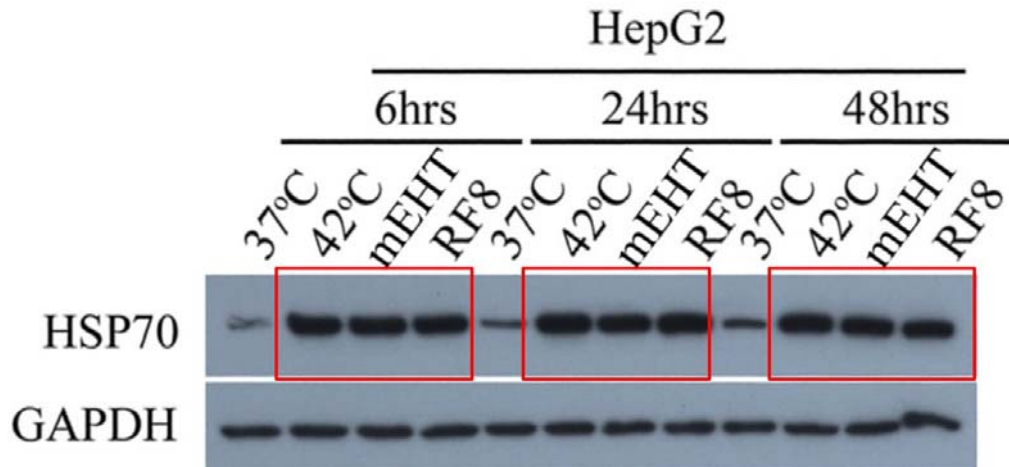
Stress protein analysis: CRT expression assay





Results

Stress protein analysis: Intracellular level of HSP70 expression

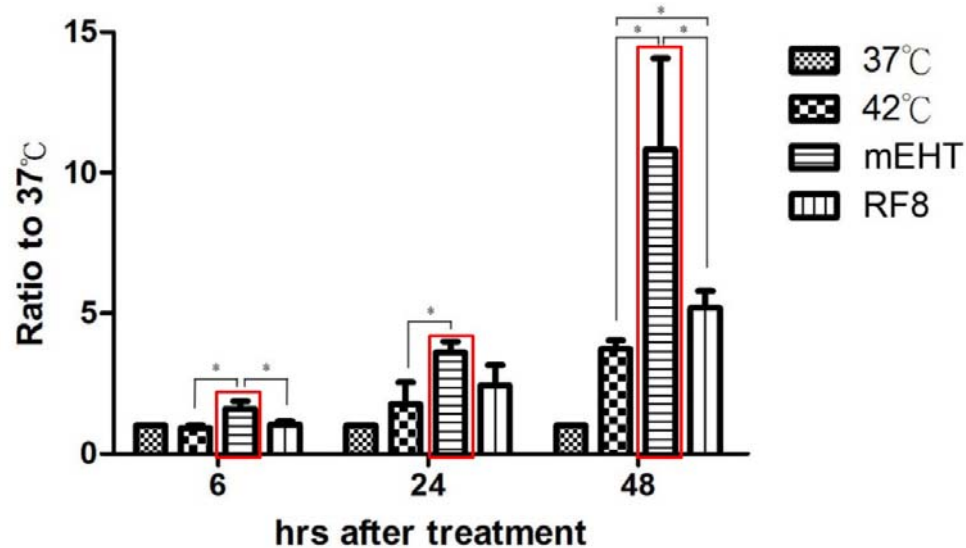


All kinds of hyperthermia could induce intracellular HSP70 expression.



Results

Stress protein analysis: HSP70 release from the cells



Oncothermia triggered a significantly secretion of HSP70 from cancer cells.

Outline

☐ Decisional points

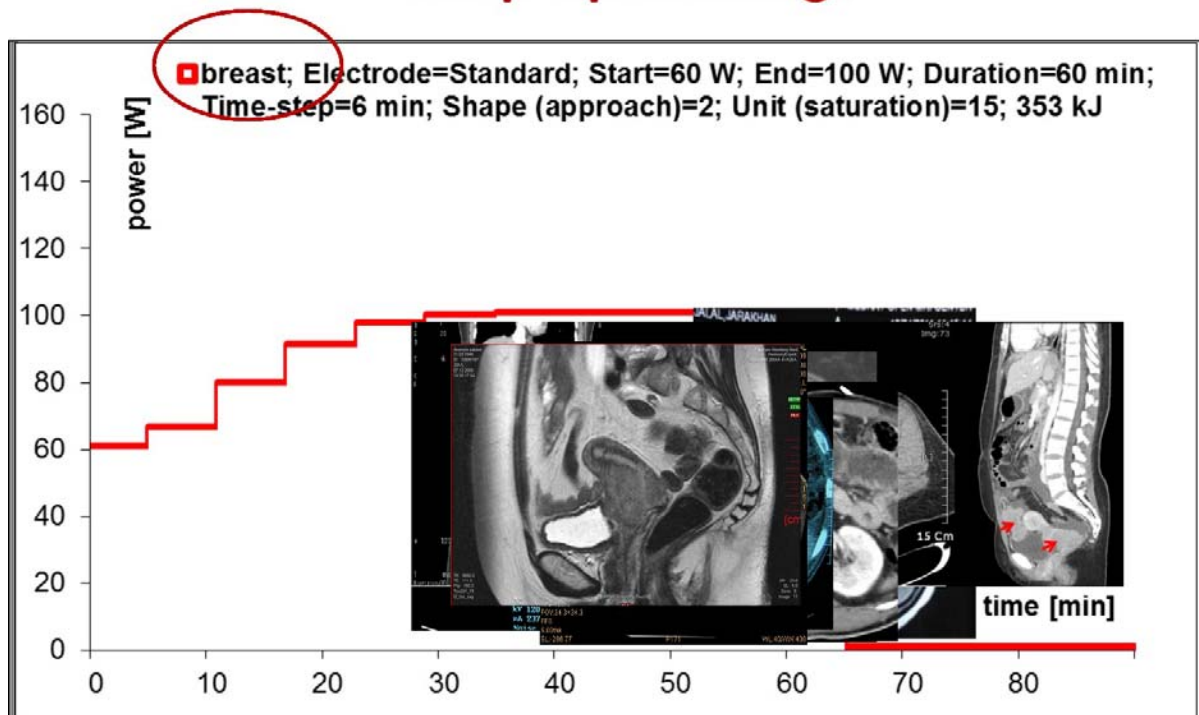
☐ Possible solution

☐ Future points

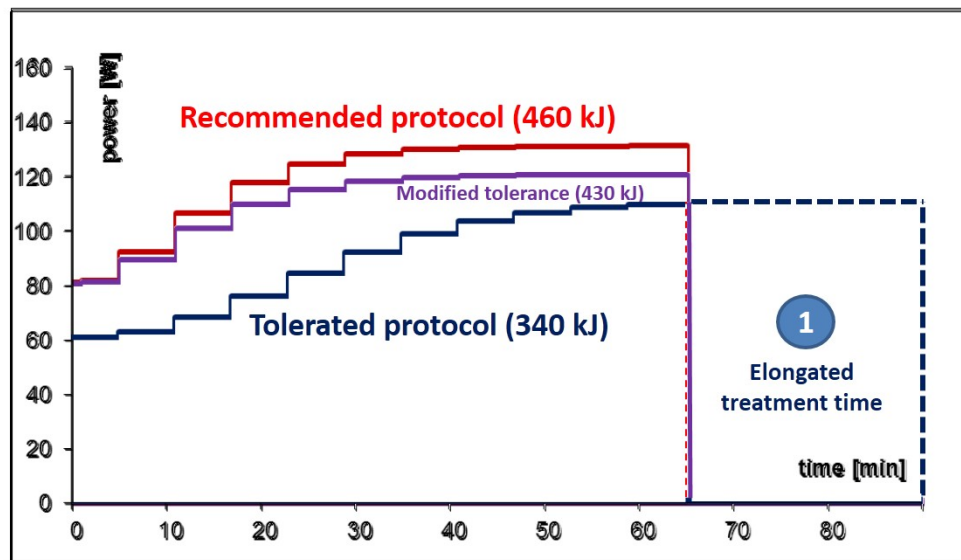
○ Take-home messages

Protocol examples with chemotherapy

Step-up heating!



Considering the personal tolerance with chemotherapy



The difference is 120 kJ

However, it could approach the recommended by increasing tolerance

2

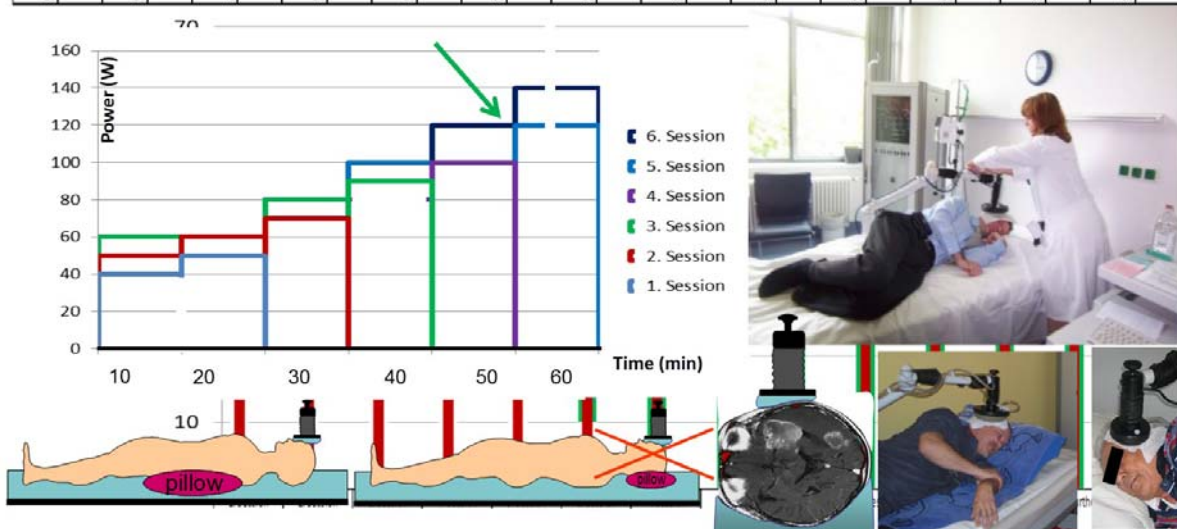
Collect the differences and correct the number of sessions with their sum!

Oncothermia for central nervous system with chemotherapy

It needs special care and protocol

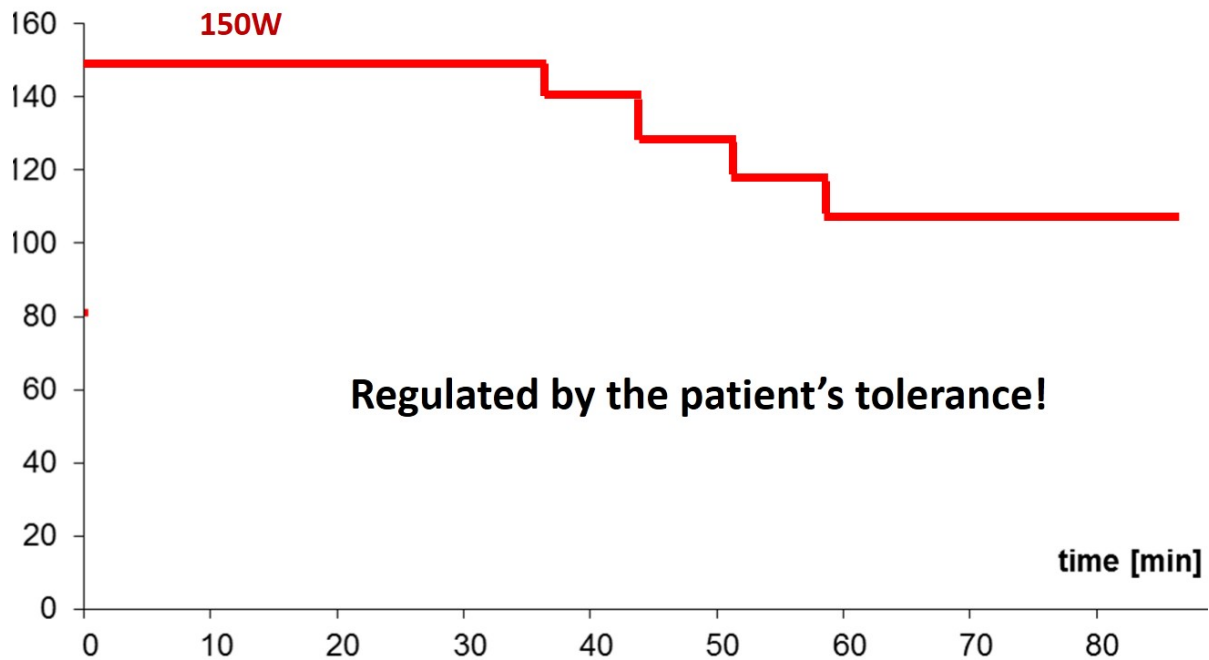
Protocol of Neurology Clinic of Medical School of Regensburg University, Germany

1. Session		2. Session		3. Session		4. Session		5. Session		6. Session		7. Session		8. Session		9. Session		10. Session		11. Session		12. Session		Further	
min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt
10	40	10	50	20	60	20	60	20	60	20	60	20	60	20	60	20	60	20	60	20	60	20	60	20	60
10	50	10	60	10	80	20	80	10	80	10	80	10	80	10	80	10	80	10	80	10	80	10	80	10	80
		10	70	10	90	10	100	20	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100	10	100
								10	120	10	120	10	120	10	120	10	120	10	120	10	120	10	120	10	120
										10	140	10	140	10	140	10	140	10	140	10	140	10	140	10	140
20		30		40		50		60		60		60		60		60		60		60		60		60	



Protocol examples in monotherapy

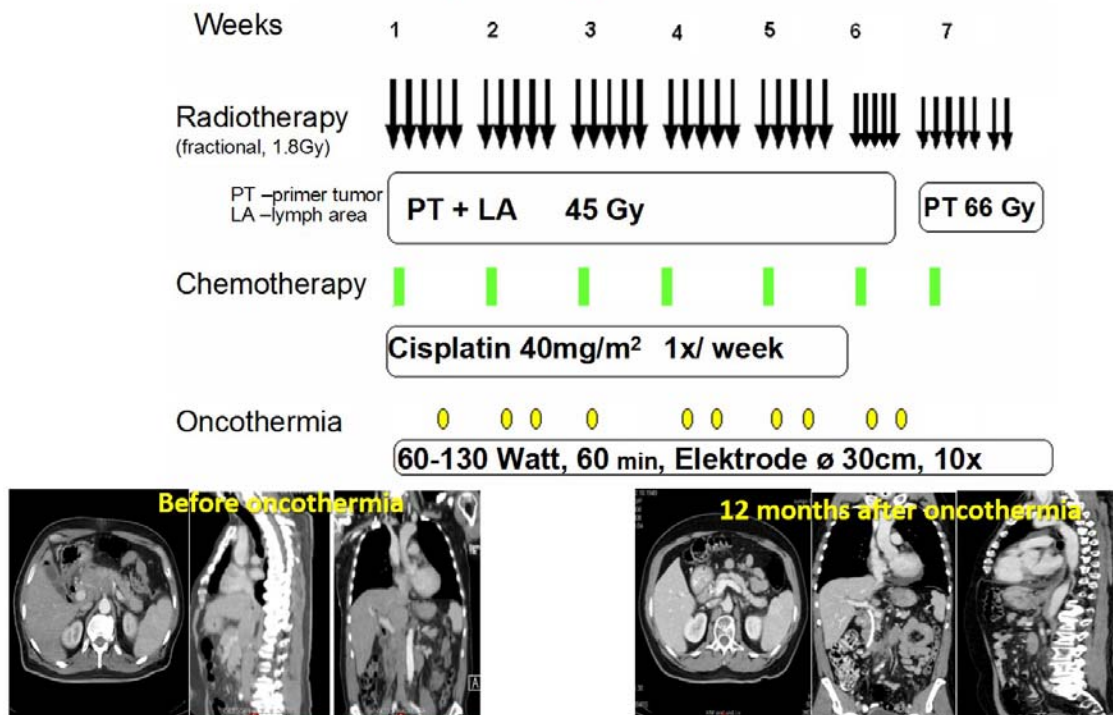
Step-down heating!



Trimodal protocol –personalized (esophagus) (2)

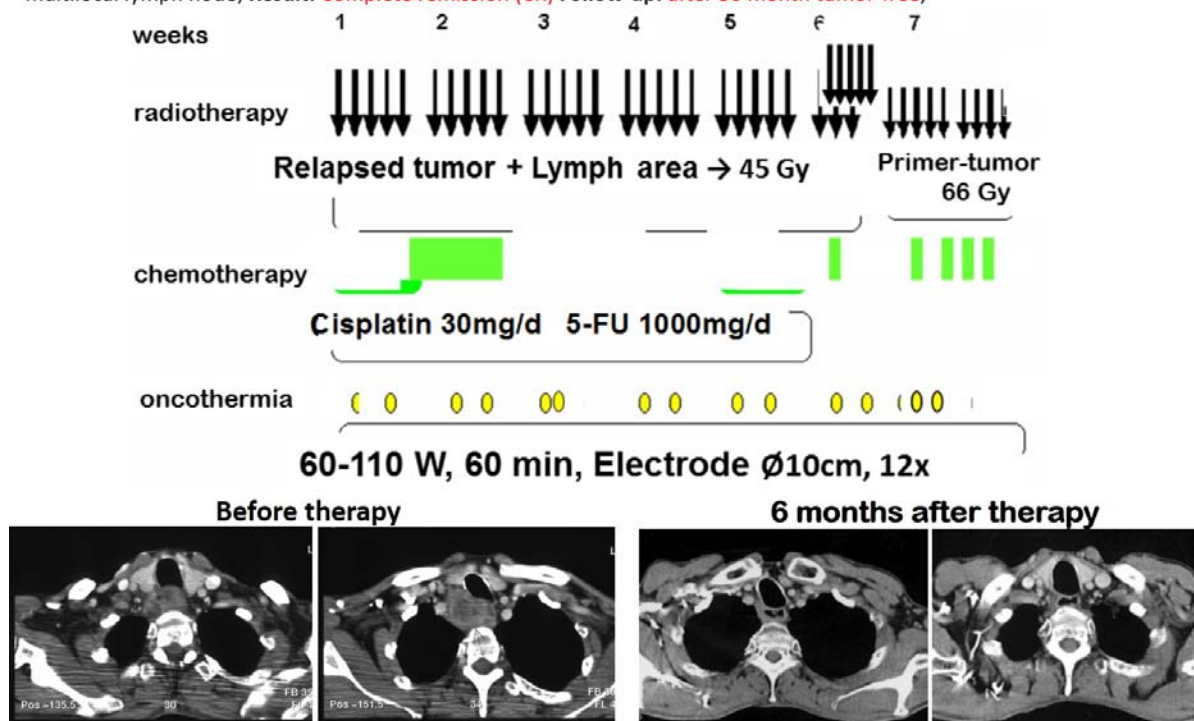
Investigator: Prof.H.Renner, Institute: Klinikum Nord, Nürnberg, Germany, Patient: G.U., 50 y, male, **Primer-tumor:** Esophagus carcinoma, inoperable; **Histology:** Squamous cell carcinoma G3; **Metastases:** in mediastinum & celiac ganglia

Tumor-classification: cT2 cN1 M1a G3 R2; **Result:** Complete remission (CR) **Follow-up:** after 12 month tumor-free



Trimodal protocol –personalized (esophagus)

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



Colorectal cancer liver metastasis, (n=15)

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

Treatment protocol in 2nd line

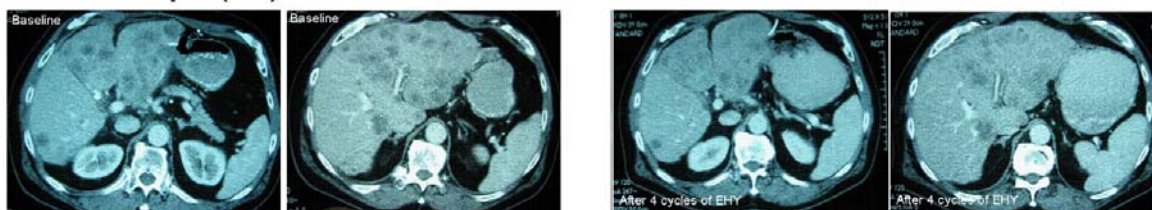
Drug	Day1	Day8	Day15	22
Irinotecan 80 mg/m ²	X	X		
Capecitabine 2 g/m ²	O O O O O O O O O O O O O			
Oncothermia	↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓			

80% local control in 2nd line
[with oncothermia combination]
(1st line was 51%,
without oncothermia)

("first line" was: Oxalyplatin & folic-acid&5-FU)

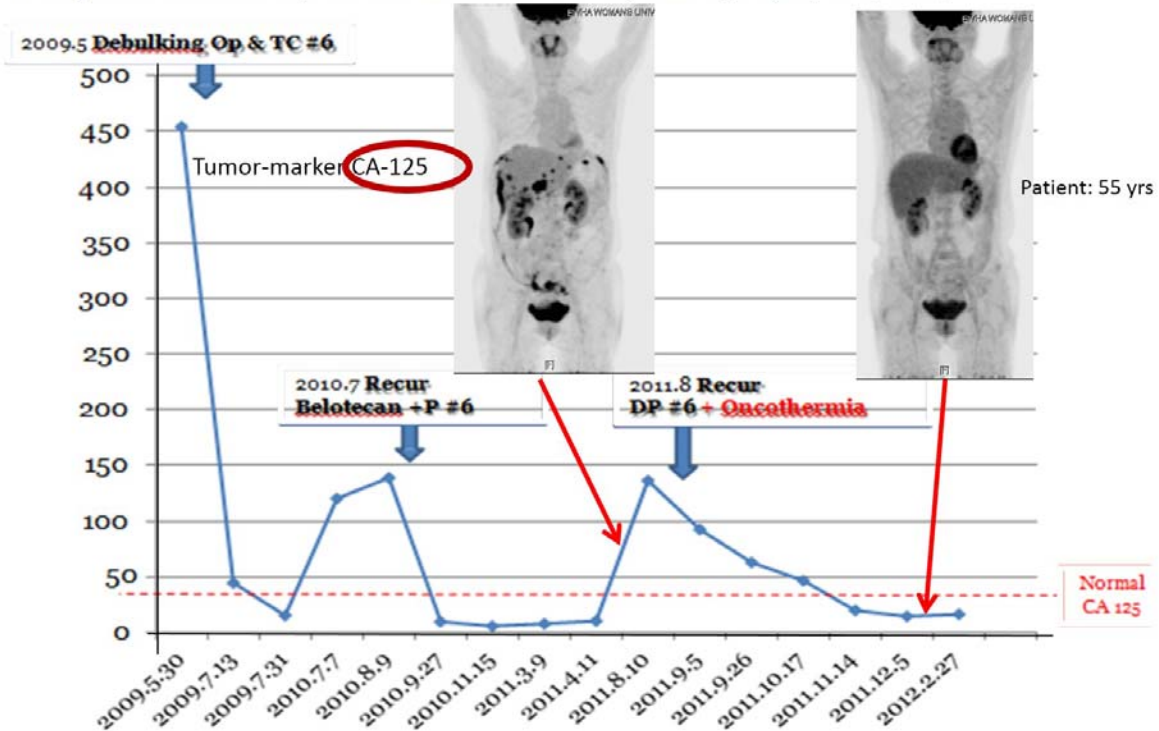
Case example (PR)

This patient died after a stable phase of 26 months (lung and brain mets.)



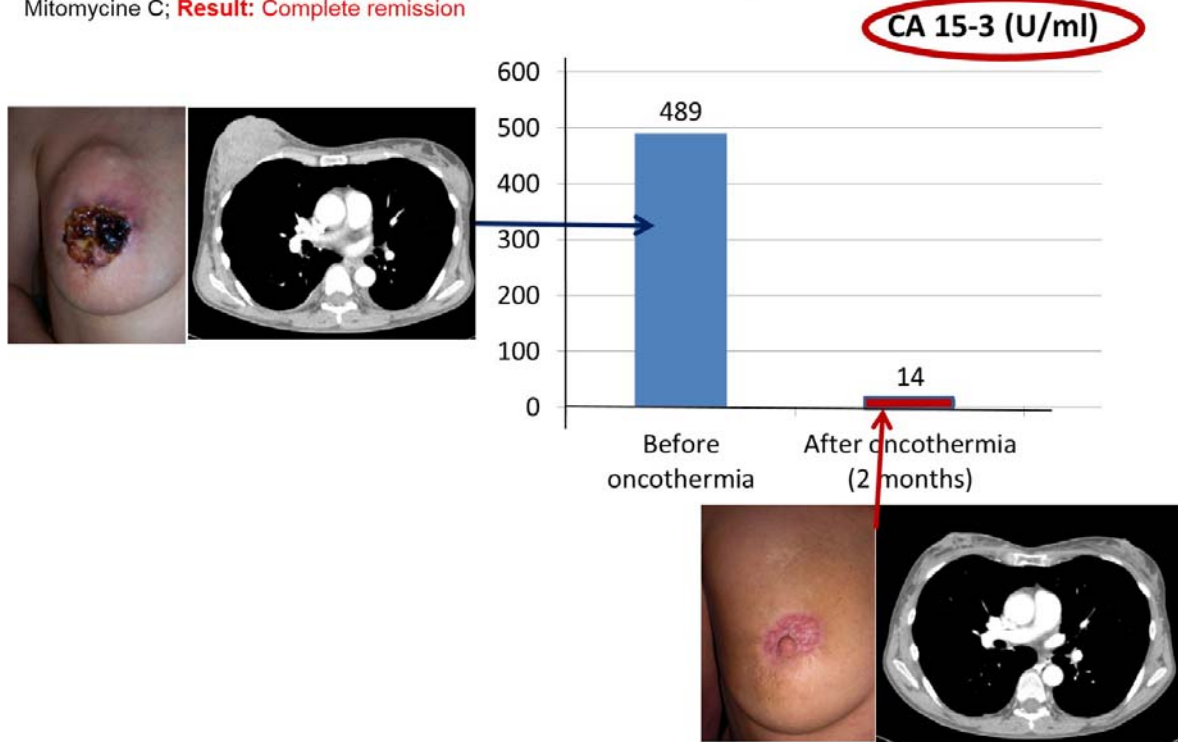
Recurrent, refractive progressive ovarian cancer

Investigator: Prof. YunHwan Kim; Institute: Ewha Womans University Mokdong Hospital, Seoul, Korea,



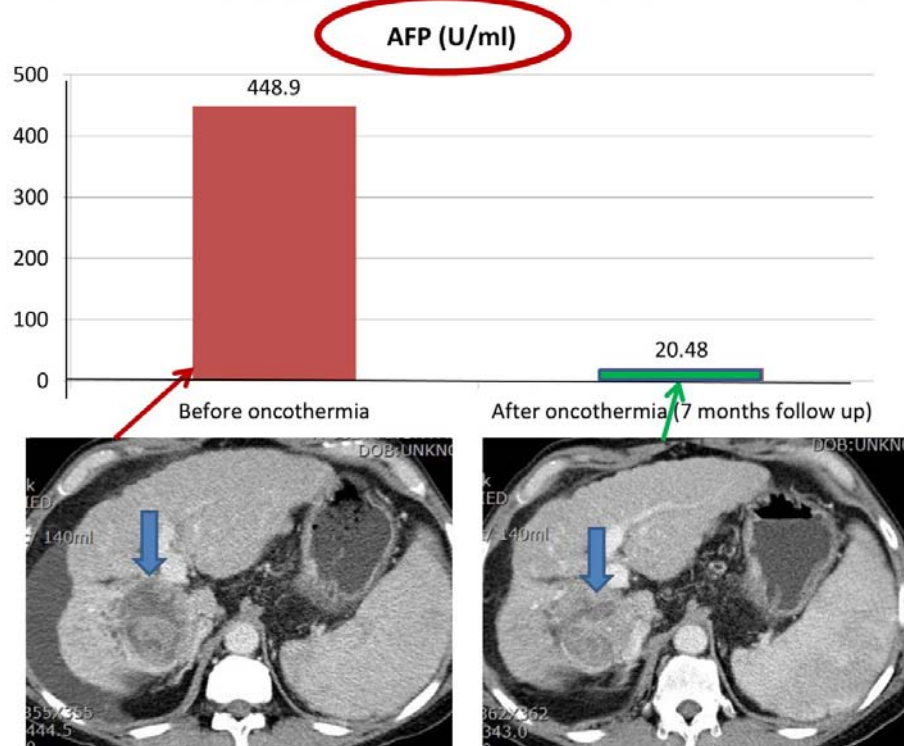
Metastatic mammary carcinoma

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



Hepatocellular carcinoma

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



Outline

☐ Decisional points

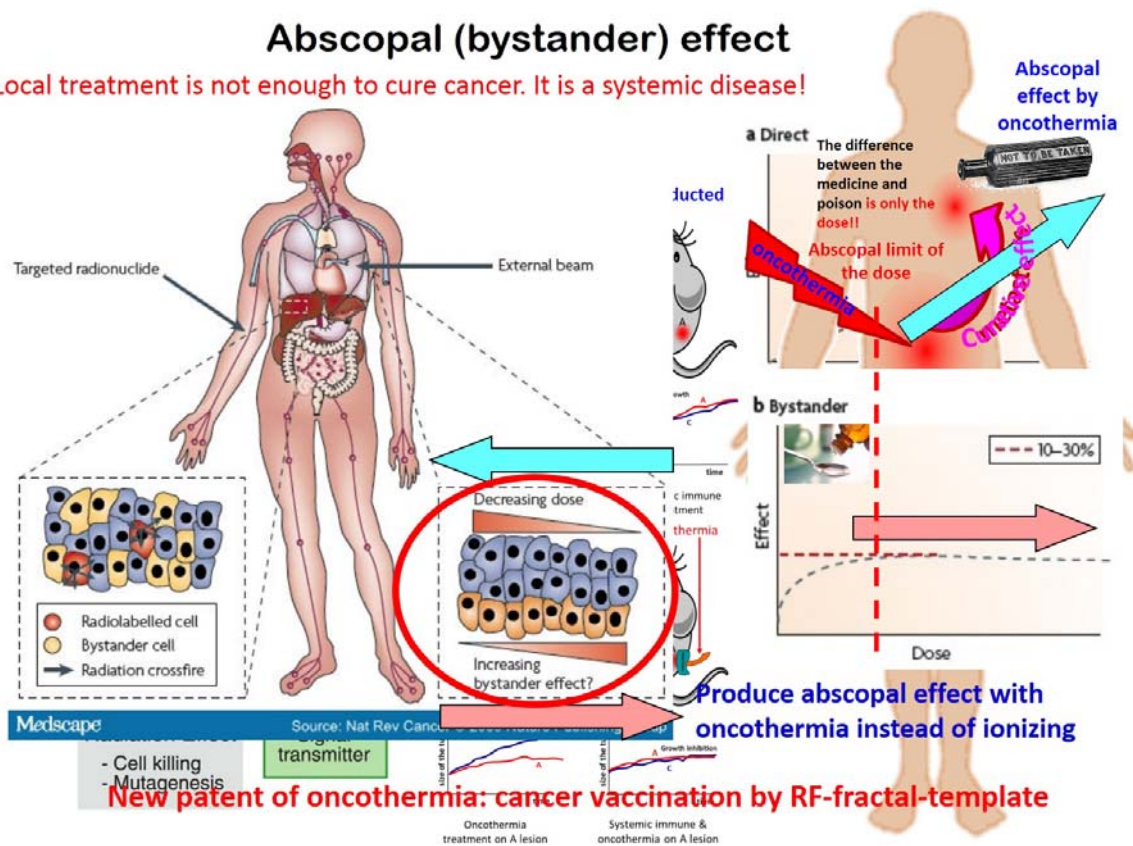
☐ Possible solution

☐ Future points

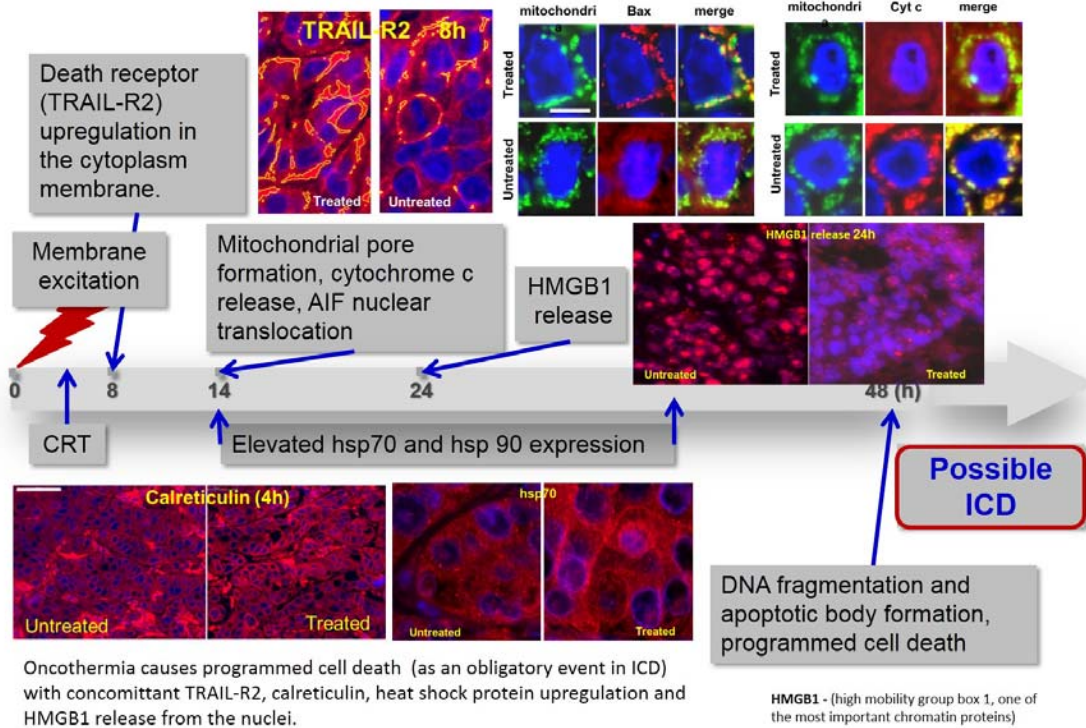
☐ Take-home messages

Abscopal (bystander) effect

Local treatment is not enough to cure cancer. It is a systemic disease!



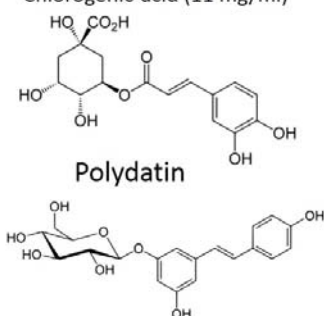
"Teach" the system resisting, DAMP generation



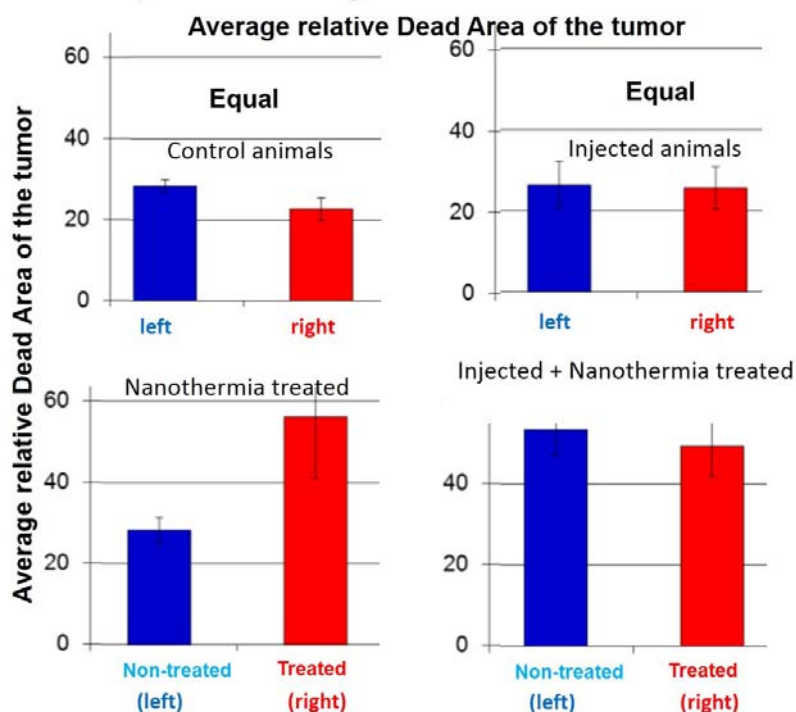


Marsdenia tenacissima
(Tongguanteng) decoctum
Injection before nanothermia

Chlorogenic-acid (11 mg/ml)



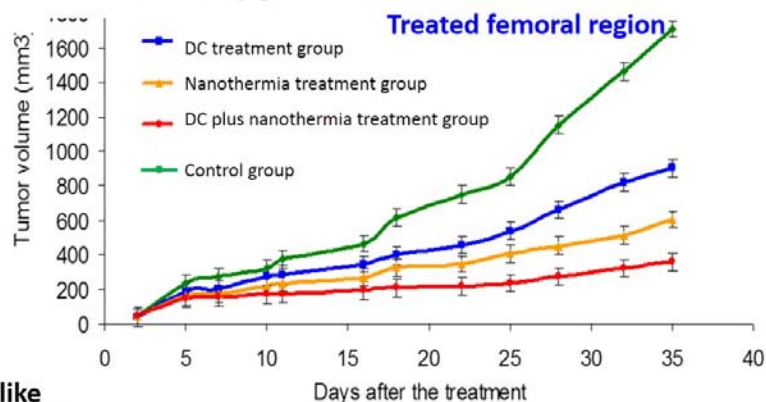
Abscopal effect by ICD



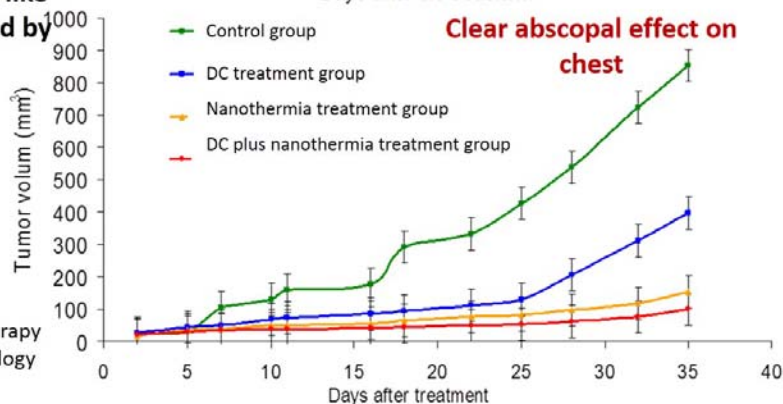
The abscopal effect is clearly proven

Nanothermia + DC therapy combination

Tumor induced on femoral
region (treated by
nanothermia)



Tumor induced on chest region like
model of metastasis, not treated by
nanothermia

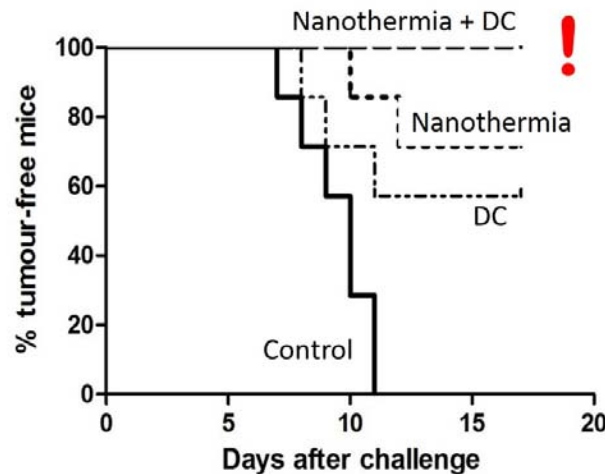


Wei Quin et.al; Modulated electro-
hyperthermia enhances dendritic cell therapy
through an abscopal effect in mice; Oncology
Reports 32: 2373-2379, 2014

Tumor growth inhibition and rechallenge inoculation

Mice were injected with 5×10^5 CT26 tumor cells s.c. in the right femoral area on the starting day and treated with nanothermia on day 14, followed by DC injection on day 15 in different groups. The data from each mouse was plotted after tumor-cell inoculation.

A secondary rechallenge with CT26 tumor cells was administered to mice 30 days after first injection as a result of either DC alone, nanothermia+DC therapy. Mice from therapy groups and untreated control BALB/c mice were inoculated subcutaneously in the left (105 parental CT26 cells) flank. (n = 7 mice per group.).



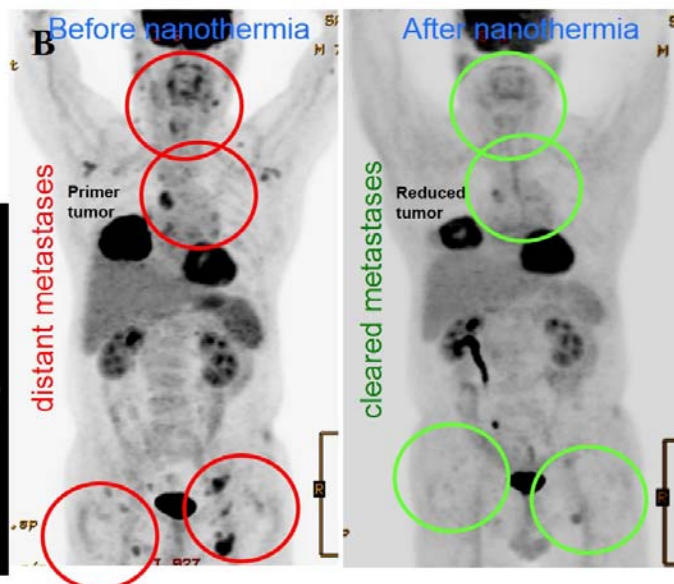
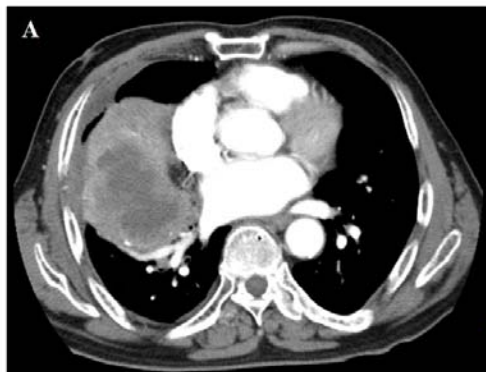
Yuk-Wah Tsang, Cheng-Chung Huang, Kai-Lin Yang, Mau-Shin Chi, Hsin-Chien Chiang, Yu-Shan Wang, Gabor Andocs, Andras Szasz, Wen-Tyng Li Kwan-Hwa Chi, Improved Immunological Tumor Microenvironment by Combined Electro-Hyperthermia followed by Dendritic Cell Immunotherapy; Cancer Immunology, Immunotherapy (submitted (2015))

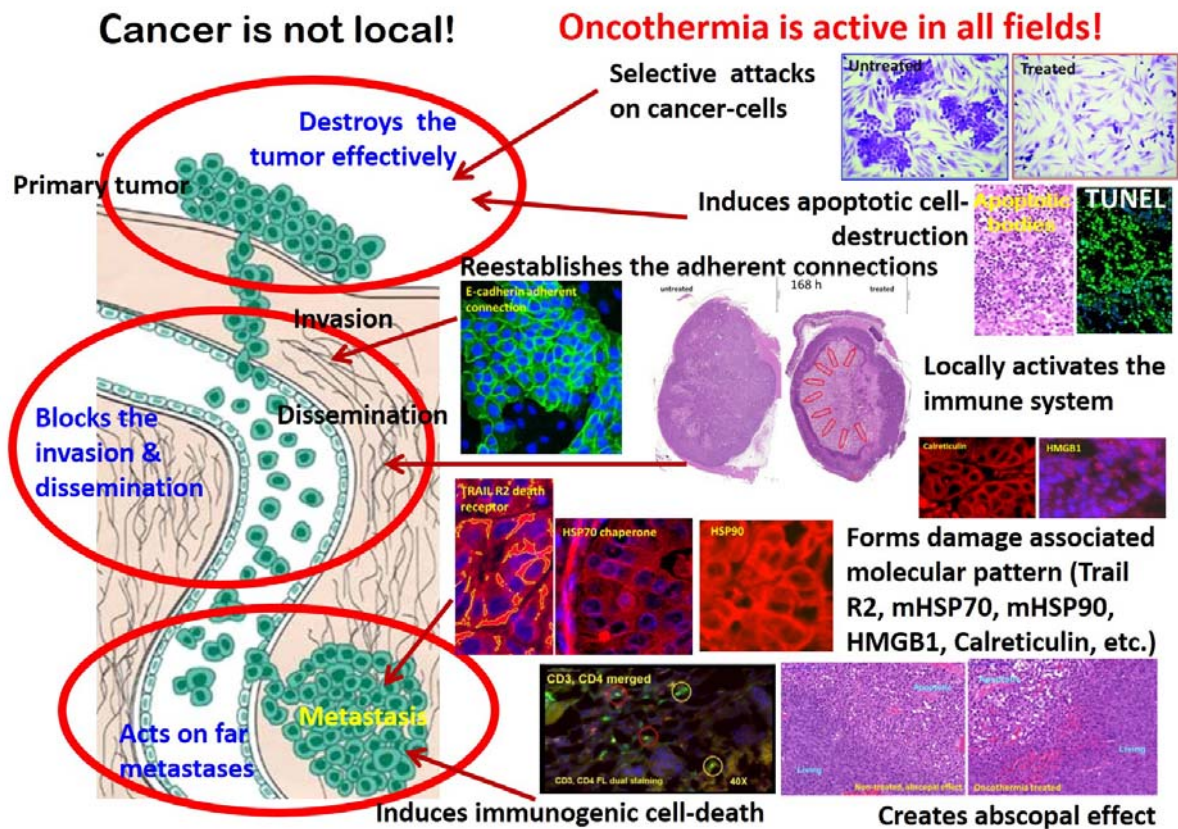
Abscopal effect

Investigator: Prof. Dr. Seong Min Yoon,
Institute: Division of Hematology-Oncology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University, Korea
Patient: 54y, male,
Primer-tumor: Non-small cell lung cancer; Size: 9.5 cm right middle lobe
Metastases: in sentinel and distant lymph-nodes
Tumor-classification: cT2 cN2 M0, stage IIIB
Treatment: trimodal protocol: 28x1.7 Gy; support: 250 microgram Leukine and Nanothermia 6x

Only the primer tumor was treated

Result: Good partial remission (PR)
Abscopal effect: complete remission (CR)
in the non treated metastatic lesions also





Outline

- ☐ Decisional points
- ☐ Possible solution
- ☐ Future points
- Take-home messages

Messages

**ONCE WE ACCEPT
OUR LIMITS, WE GO
BEYOND THEM.**



Albert Einstein

German Theoretical-Physicist
(1879-1955)

QuoteHD.com

**We can't solve
problems by using the
same kind of thinking
we used when we
created them.**



Albert Einstein

German Theoretical-Physicist
(1879-1955)

QuoteHD.com

Have we recognized our limits?

Do we think differently?

Thank you for your attention

biotech@gek.szie.hu

**The place and role of clinical hyperthermia in oncological
thermotherapy: let's define what we are talking about**

Sergey V. Roussakow*

* Galenic Research Insitute

The place and role of clinical hyperthermia in oncological thermotherapy: let's define what we are talking about

Sergey V. Roussakow

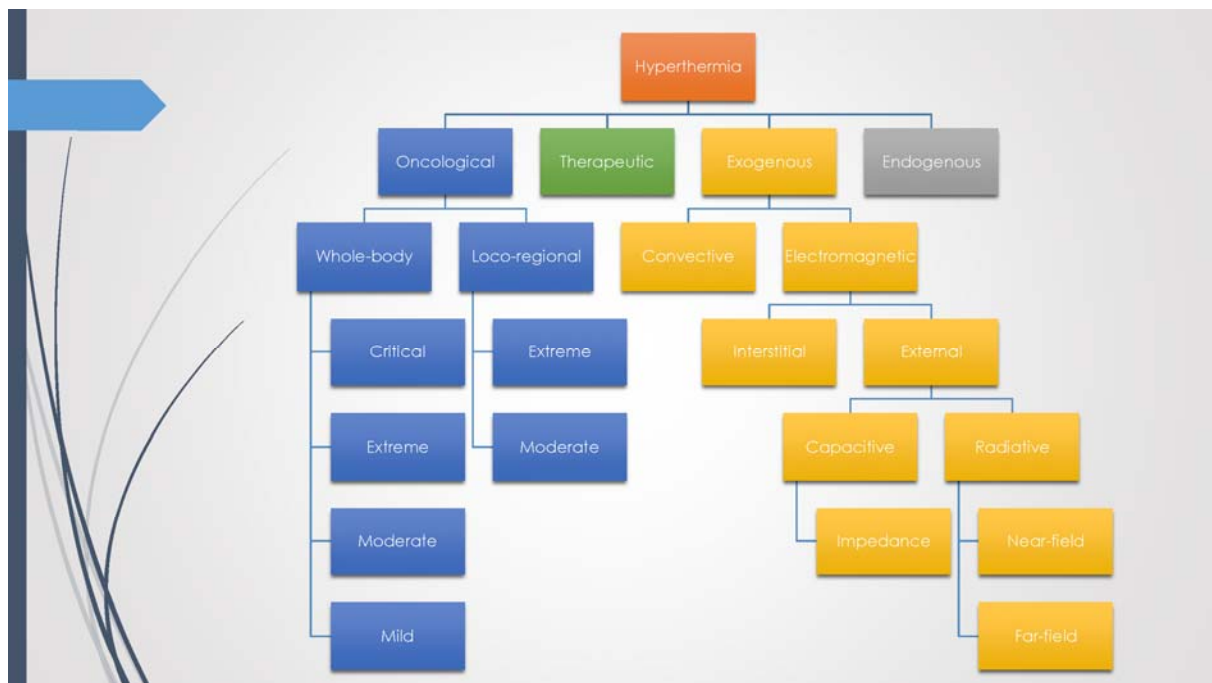
Galenic Research Institute

34th Annual Conference of the International Clinical Hyperthermia Society

Pesaro, Italy

22nd September 2016

T, °C	Type of Thermal Therapy	Type of Tumor Damage	Effect to Cells and Tissues		
			Tumor	Healthy	
100			Carbonization		
85	Thermal Ablation (TA)	Acute Damage (<15')	Direct Cell Damage (Protein Denaturation)		
75					
65					
60	High-Intensity Thermal Therapy (HITT)	Sub-Acute Damage (15-90')	Indirect Cell Damage		
55					
50			Therapeutic Hyperthermia		
45					
44	Oncological Hyperthermia (OHT)	Delayed Damage (days)	Improvement of Tissue Trophism		
43					Critical OHT
42					Extreme OHT
41	Moderate OHT				
40	Febrile Therapy (Mild HT)				
39					
38	Subfebrile Range	No Damage or Tumor Growth Stimulation			
37					
	Normothermia	No	No		

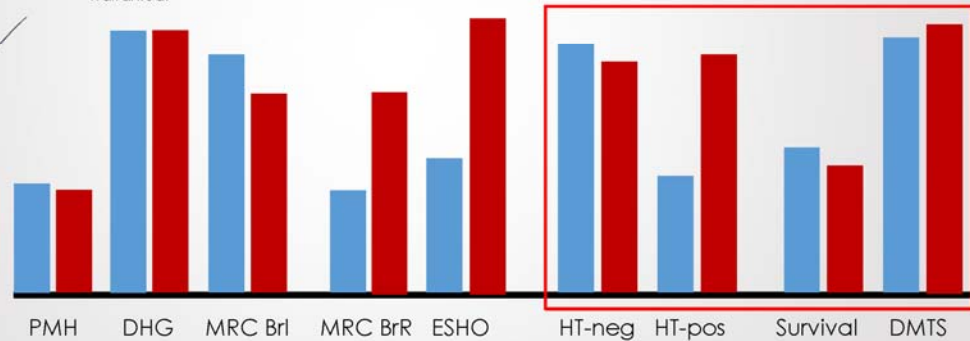


THE PROBLEM OF HYPERTHERMIA:
IT DIES

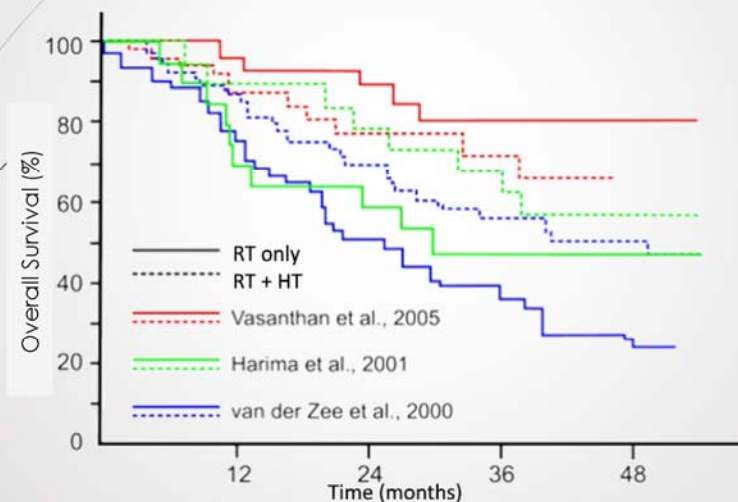
RADIOTHERAPY WITH OR WITHOUT HYPERTHERMIA IN THE TREATMENT OF SUPERFICIAL LOCALIZED BREAST CANCER: RESULTS FROM FIVE RANDOMIZED CONTROLLED TRIALS

INTERNATIONAL COLLABORATIVE HYPERTHERMIA GROUP (Vernon et al., 1996)

- The overall CR rate for RT alone was 41% and for combined treatment arm was 59%, giving an odds ratio of 2.3.
- Not all trials demonstrated an advantage for the combined treatment.
- The implication of these encouraging results is that hyperthermia appears to have an important role in the clinical management of this disease, and there should be no doubt that further studies of the use of hyperthermia are warranted.

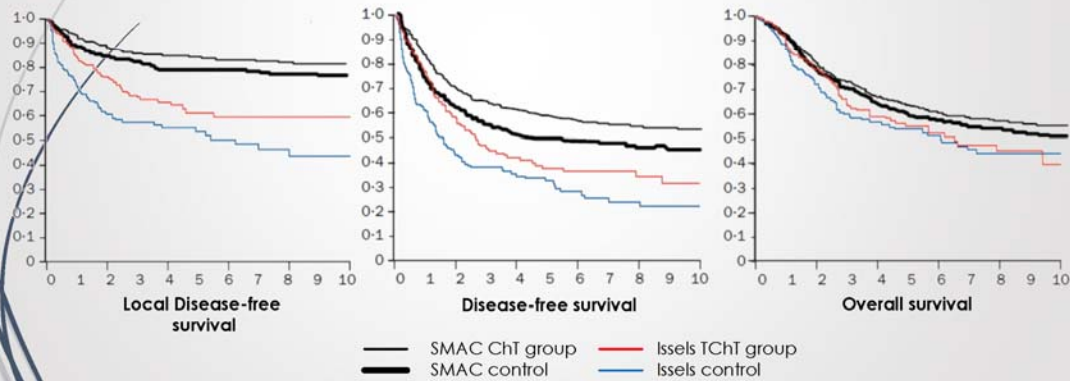


Hyperthermia at cervical cancer: the results of three randomized trials.

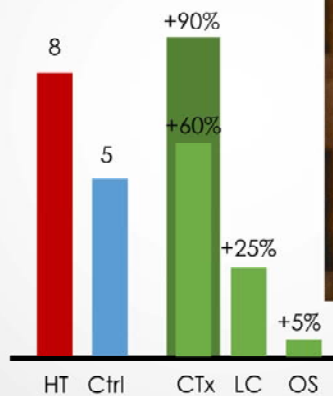
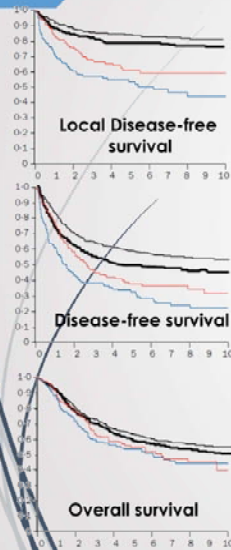


Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)

To our knowledge, this is the first randomised phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Adding regional hyperthermia to chemotherapy is a new effective treatment strategy for patients with high-risk STS, including STS with an abdominal or retroperitoneal location.



Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)



ORIGINAL ARTICLE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Margaret Wenz, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthony, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Jensen, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*

ABSTRACT

BACKGROUND

There is no established standard chemotherapy for patients with locally advanced or metastatic biliary tract cancer. We initially conducted a randomized, phase 2 study involving 80 patients to compare cisplatin plus gemcitabine with gemcitabine alone. After we found an improvement in progression-free survival, the trial was extended to the phase 3 trial reported here.

METHODS

We randomly assigned 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin (75 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4 weeks for six cycles) for up to 24 weeks. The primary end point was overall survival.

RESULTS

After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin-gemcitabine group and 8.5 months among the 206 patients in the gemcitabine group (hazard ratio, 0.84; 95% confidence interval, 0.52 to 0.80, $P=0.003$). The median progression-free survival was 8.0 months in the cisplatin-gemcitabine group and 5.0 months in the gemcitabine group ($P=0.001$). In addition, the rate of tumor-related adverse events in the cisplatin-gemcitabine group was significantly increased (81.4% vs. 71.8%, $P=0.009$). Adverse events were similar in the two groups, with the exception of severe neutropenia in the cisplatin-gemcitabine group; the number of neutropenia-associated infections was similar in the two groups.

CONCLUSIONS

As compared with gemcitabine alone, cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity. Cisplatin plus gemcitabine is an appropriate option for the treatment of patients with advanced biliary cancer. (ClinicalTrials.gov number, NCT00629563.)

N Engl J Med 2010; 363:1231-41. DOI: 10.1056/NEJM.2010.06.01.1000000

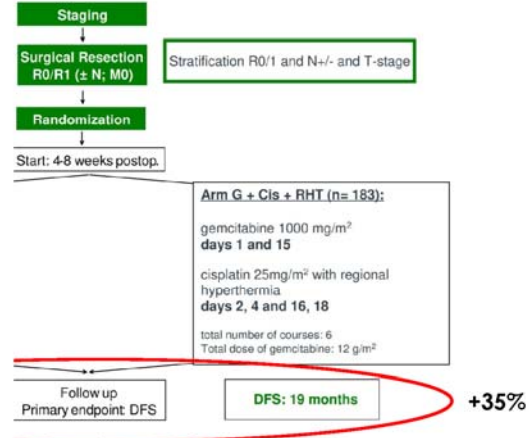
The New England Journal of Medicine
Downloaded from www.nejm.org on July 18, 2010. For personal use only. No other uses without permission.
Copyright © 2010 Massachusetts Medical Society. All rights reserved.

European Adjuvant Trial (HEAT)

randomized phase III clinical trial

Number: 2008-004802-14

able Pancreatic Cancer



Additive effect of cisplatin plus hyperthermia

Hyperthermic potentiation of cis-diamminedichloroplatinum (II) cytotoxicity in Chinese hamster ovary cells resistant to the drug

Wallner KE, DeGregorio MW, Li GC
Cancer Res. 1986

The cytotoxic effect of cis-diamminedichloroplatinum (II) on cultured Chinese hamster ovary cells at elevated temperatures: Arrhenius plot analysis

Urano M, Kahn J, Majima H, Gerweck LE
Int J Cancer 1995

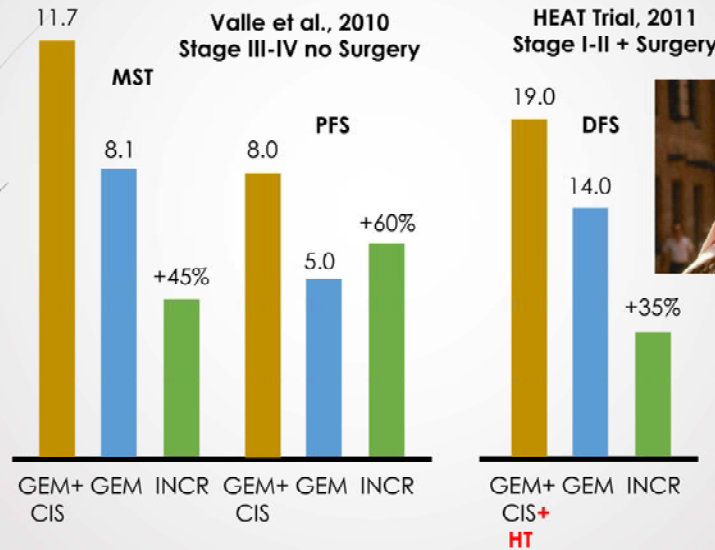
Enhancement of cisplatin sensitivity and platinum uptake by 40 degrees °C hyperthermia in resistant cells

Ohtsubo T, Saito H, Tanaka N, Matsumoto H, Sugimoto C, Saito T, Hayashi S, Kano E
Cancer Lett. 1997

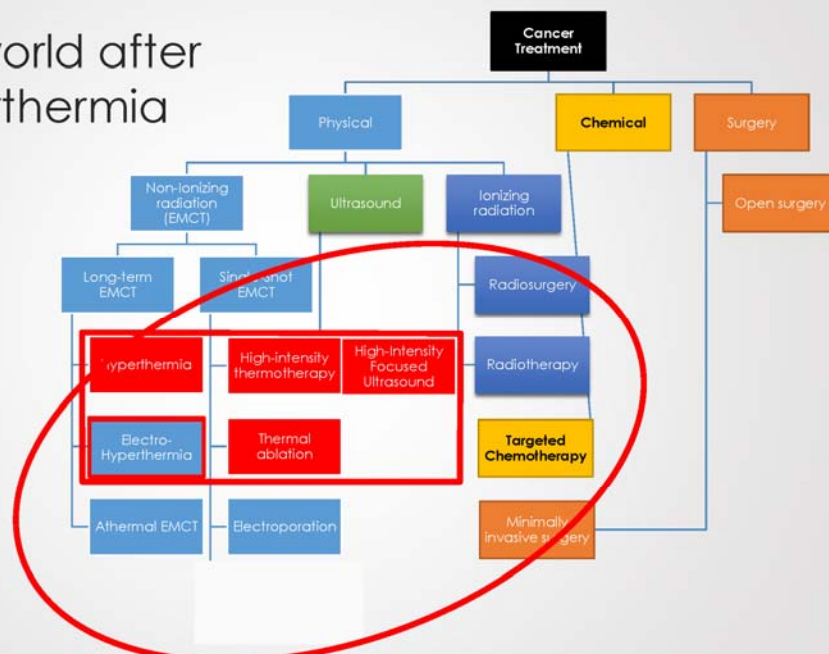
Cisplatin sensitization by concurrent mild hyperthermia in parental and mutant cell lines deficient in homologous recombination and non-homologous endjoining repair.

Raaphorst GP, Li LF, Yang DP, LeBlanc JM
Oncol Rep 2005

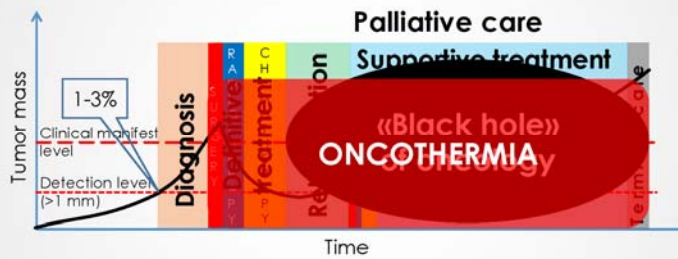
Manufacturing Hyperthermia "Positive" Results: the inner kitchen on the example of HEAT trial



The world after hyperthermia



Oncothermia application range



The Future of Cancer Treatment



Thank you for attention



Huigol trial

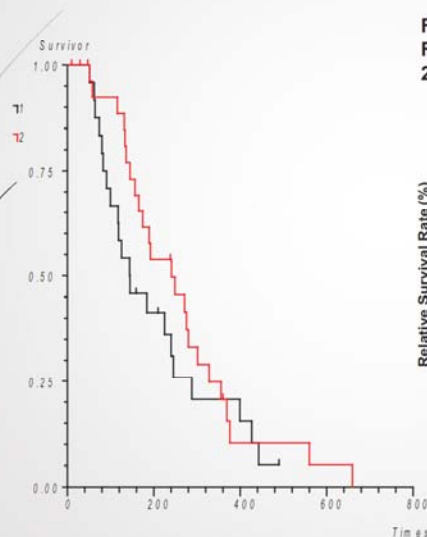
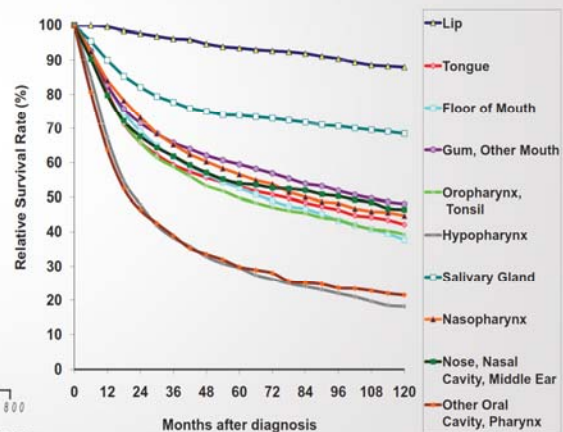


Figure 2.1: Cancer of the Head and Neck: Relative Survival Rate (%) by Primary Site, Ages 20+, 12 SEER Areas, 1988-2001



Huigol trial

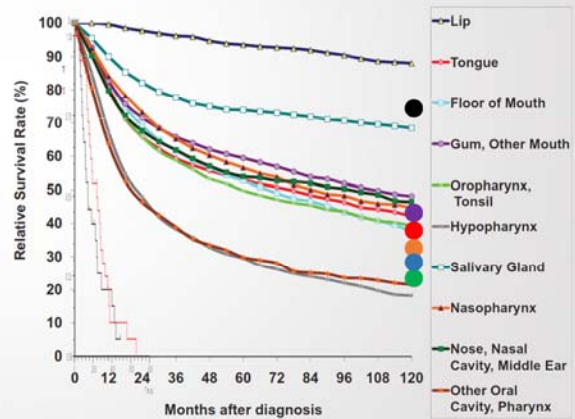
"The 5-year relative survival rates were 74.5% for the lip, 42.7% for the anterior tongue, 25.5% for the posterior tongue, 45.1% for the mouth, 29.7% for the oropharynx, 38.7% for the nasopharynx, 29.1% for the hypopharynx, and 41.2% for the larynx." (Mumbai 1987-1991).

Yeole BB, Sankaranarayanan R, Sunny M Sc L, Swaminathan R, Parkin DM. Survival from head and neck cancer in Mumbai (Bombay), India. *Cancer*. 2000 Jul 15;89(2):437-44.

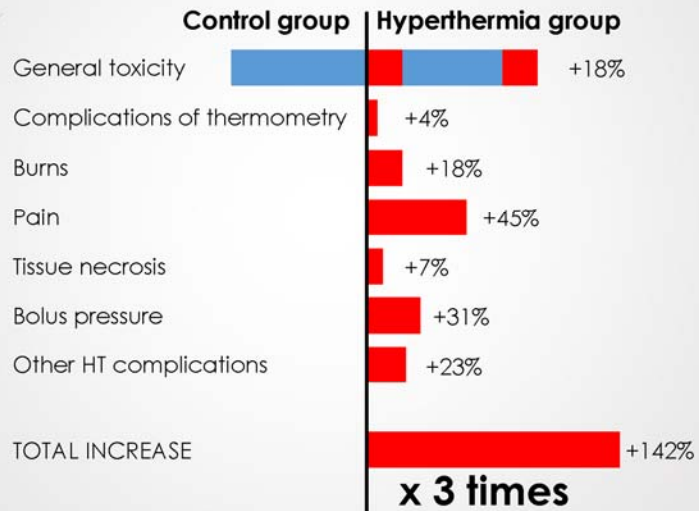
"The overall 5-year survival rate was in the range of 20-43% for oral cancer, 8-25% for pharyngeal cancers and 25-62% for laryngeal cancer." (Mumbai, 1987-1989; 25% of stage IV).

Rao DN, Shroff PD, Chattopadhyay G, Dinshaw KA. Survival analysis of 5595 head and neck cancers—results of conventional treatment in a high-risk population. *Br J Cancer*. 1998 May; 77(9): 1514-1518.

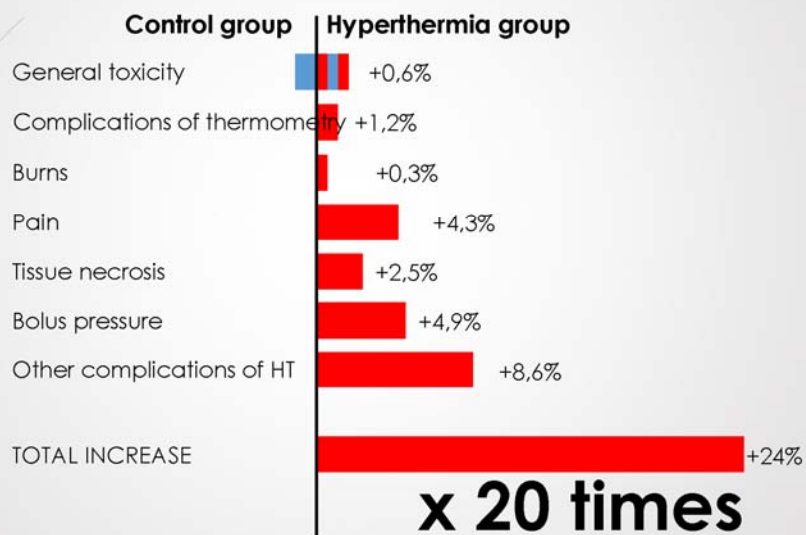
Figure 2.1: Cancer of the Head and Neck: Relative Survival Rate (%) by Primary Site, Ages 20+, 12 SEER Areas, 1988-2001



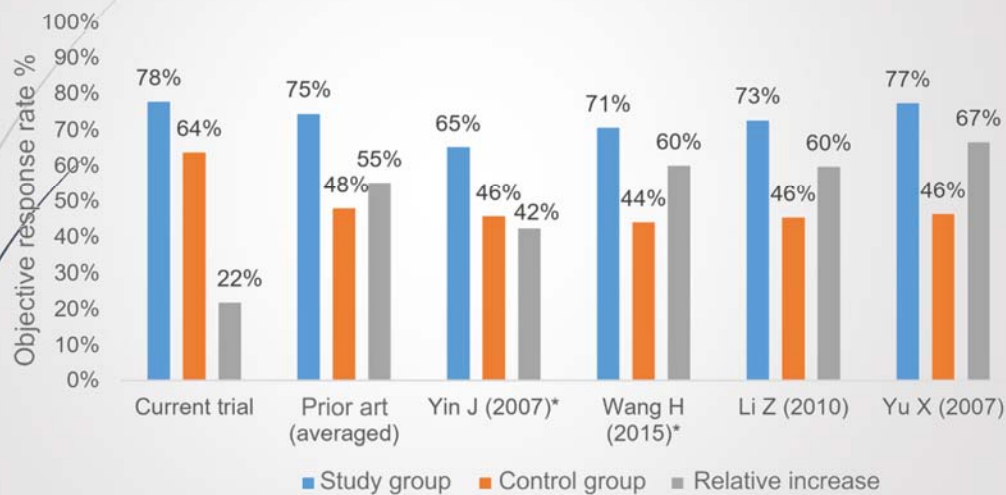
Estimation of general toxicity



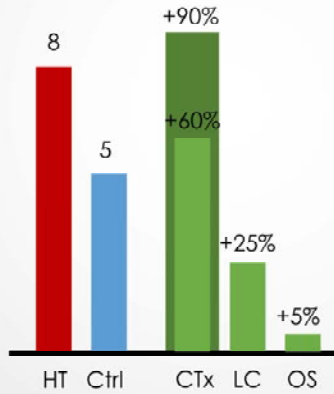
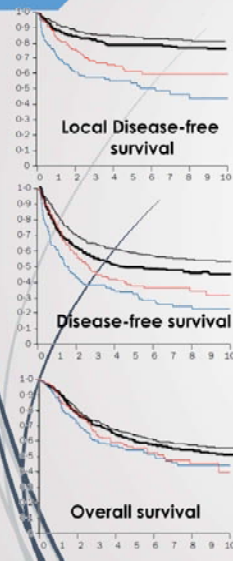
Estimation of severe toxicity



Prof. Pang trial

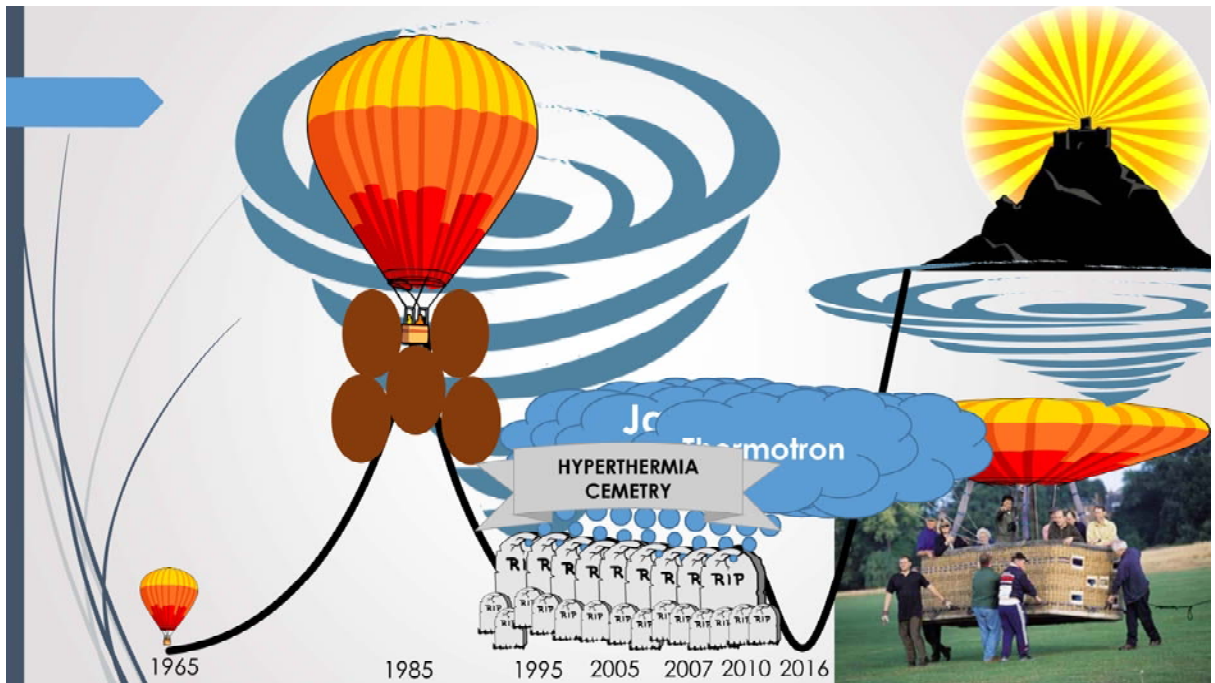


Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)



Where is hyperthermia?





**Pharmacoeconomic study of oncothermia (modulated
electro-hyperthermia) in the treatment of lung cancer**

Sergey V. Roussakow*

* Galenic Research Institute

Pharmacoeconomic study of oncothermia (modulated electro-hyperthermia) in the treatment of lung cancer

Sergey V. Roussakow

Galenic Research Institute

34th Annual Conference of the International Clinical Hyperthermia Society

Pesaro, Italy

22nd September 2016

Pre-requisites of the study

- Lung cancer is a fatal disease with one of the least 5-year survivals among all cancers (14-17% in USA and 12-14% in EU).
- In Russia (2012), share of lung cancer is 18,7% in men and 3,6% in women, and it is the first reason of cancer mortality in Russia (17,3% of all cancer deaths).
- Current treatments show low efficacy and can't change the trend of high mortality.
- Thus, study of possibilities to improve the prognosis in lung cancer is of outstanding significance in oncology.



Oncothermia solution

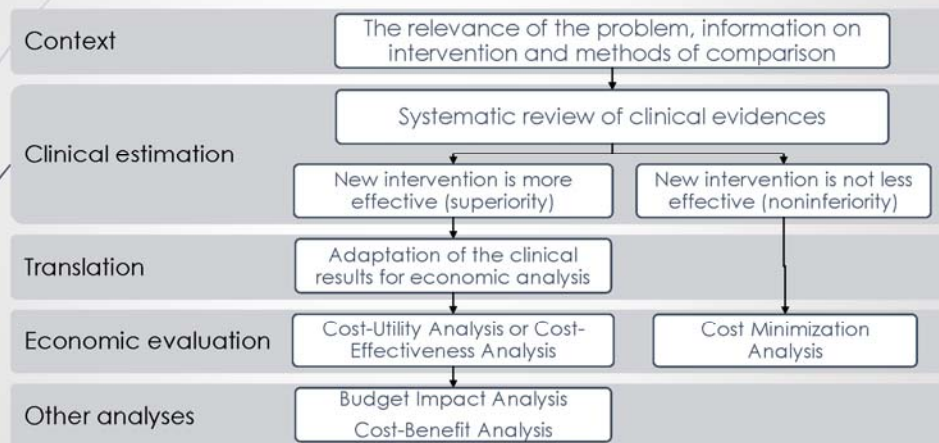
- Oncothermia (local, deep, radiofrequency, modulated electro-hyperthermia) is one of the promising methods of lung cancer treatment.
- This is a new technology based on the local effect of high-frequency electromagnetic field (13.56 MHz), modulated by fractal noise in a range 0-5 kHz, performed by capacitive coupling and functionally asymmetric electrodes.
- The relevance of the present study is determined by the possibility to improve the quality of treatment of lung cancer while reducing health care costs.



Methods

- Retrospective pharmacoeconomical observational study
- Systematic review of oncothermia trials on lung cancer treatment
- Cost-Utility Analysis
- Budget Impact Analysis

Structure of Study



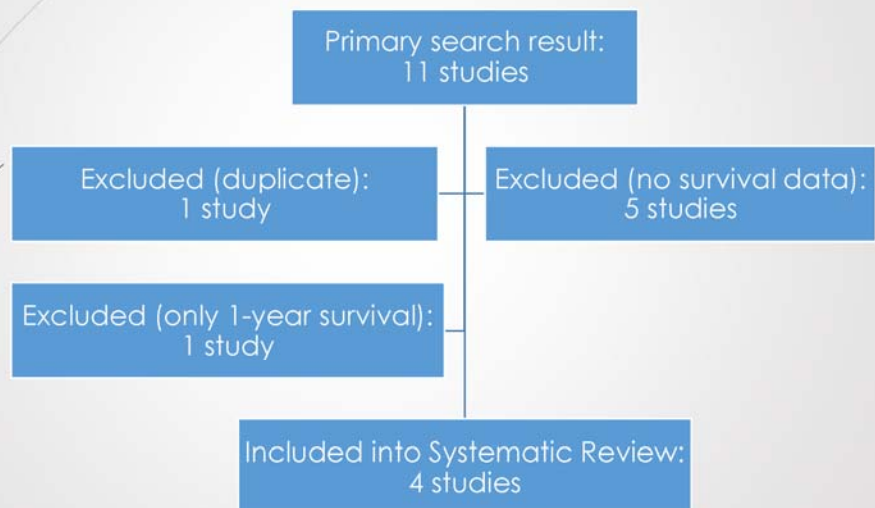
Systematic review

- In accordance with PRISMA and CHSRI recommendations.
- Search by keywords: ([oncothermia] OR [electro-hyperthermia] OR [electrohyperthermia] OR ([electro] AND [hyperthermia])) AND ([lung cancer] OR [C34] OR ([lung] AND [cancer]) OR [lung tumor])
- Databases:
 - US NIH (<http://clinicaltrials.gov/>)
 - EudraCT (<https://www.clinicaltrialsregister.eu/>)
 - UMIN (<http://rctportal.niph.go.jp/>)
 - MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>)
 - Cochrane Library (<http://www.cochranelibrary.com/>)
 - BMC (<http://www.biomedcentral.com/>)
 - Wiley Online Library (<http://onlinelibrary.wiley.com/>).
- Other sources:
 - Oncothermia Journal (<http://www.oncothermia-journal.com/journal/>)
 - Conference Papers of ICHS, DGH, ESHO, STM, JSHO

Systematic Review: Endpoints

- Primary Endpoints:
 - Overall Survival
- Secondary Endpoint:
 - Health-related Quality of Life (for QALY calculation)

Search Flowchart



Systematic Review: Accepted Studies

Name of Study	Country	Type	NOP	LOE	Publication
Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer	Korea	Prospective, cohort, phase II	31	2b	Lee DY, Haam SJ, Kim TH, Lim JY, Kim EJ, Kim NY. Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer. Conference Papers in Medicine. 2013: Article ID 910363, 7 p. doi:10.1155/2013/910363.
Clinical study for advanced non-small-cell lung cancer treated by oncothermia	Hungary	Retrospective, cohort, phase II	258	2c	Dani A, Varkonyi A, Magyar T, Szasz A. Clinical study for advanced non-small-cell lung cancer treated by oncothermia. Oncothermia J. 2011;3:39-49.
Retrospective matched-group clinical study for advanced NSC lung cancer	Hungary		186	2c	Dani A, Osvath M, Szasz A, Szasz N. Retrospective matched-group clinical study for advanced NSC lung cancer. Hyperthermia symposium Cologne, October 24-25, 2003.
A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting	Canada		48	2c	Parmar G. A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting. XXXIII Annual Conference of the International Clinical Hyperthermia Society (ICHS). 10-12 Jul 2015, Nidda, Germany.
TOTAL:			458	2a	

CEBM Levels of Evidence (2016)

Level	Interventional Studies
1a	Systematic reviews (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
2a	Systematic reviews (with homogeneity) of Cohort Studies
2b	Individual Cohort Study (including low quality RCT)
2c	"Outcomes" Research
3a	SR (with homogeneity) of Case-Control Studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"



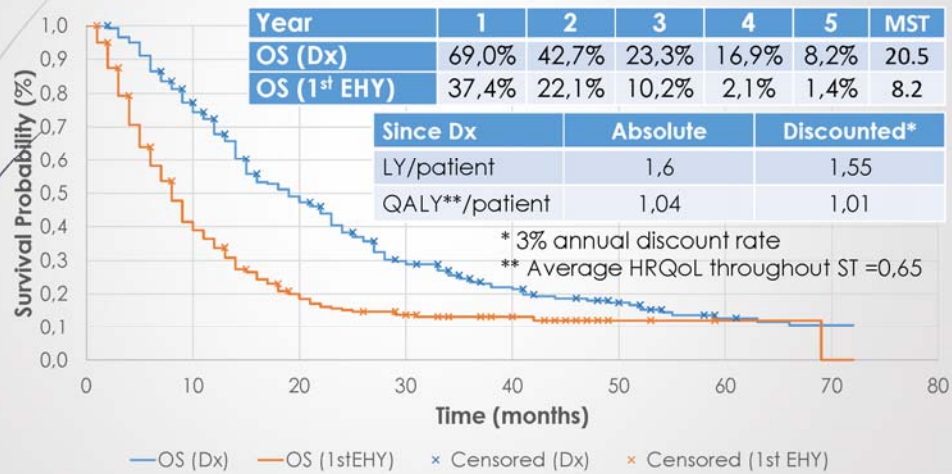
Analysis of Evidences



Study 1 (Dani et al., 2011): Description

- Retrospective, 2-center, cohort, single arm study
- Non-small cell lung cancer (N=258):
 - Peterfy Hospital (Budapest) (PFY, n=61)
 - HTT-Med Clinic (Budapest) (HTT, n=197)
- Recruitment period: Oct 1997 - Dec 2003
- Average age 57.2 ± 0.65 yrs, median 57 yrs (16-84), normal distribution
- Gender structure: 67.8% males
- Inoperable (St. IIIB-IV): 29% at Dx, 75% at 1st EHY (61% St. IV)
- Oncothermia included in the complex treatment
- Average time to start of oncothermia 11.9 ± 1.07 m, median 6.2 m (0.2-142) or $49.8\% \pm 1.8\%$ of OS, median 50.7% (0.68-99)
- Oncothermia applied in the III quartile of survival time

Study 1 (Dani et al., 2011): Survival



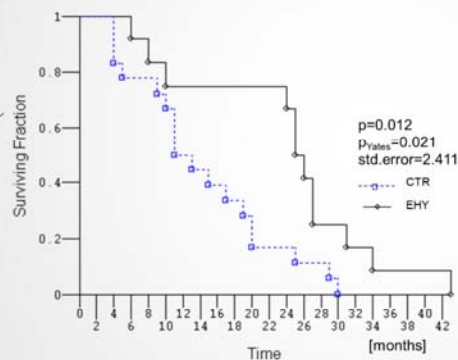
Study 1 (Dani et al., 2011): Quality Control

- Full sample (no exclusions or extractions) – confirmed by check of primary trial documentation
- No inclusion criteria (not limited by Age, Stage of disease or performance status)
- Censoring rate 19% (48/258):
 - Lost during follow-up 11% (28/258)
 - Right-censored (alive to the end of the trial) 8% (20/258)
- Exact death determination by Hungarian Civil Register

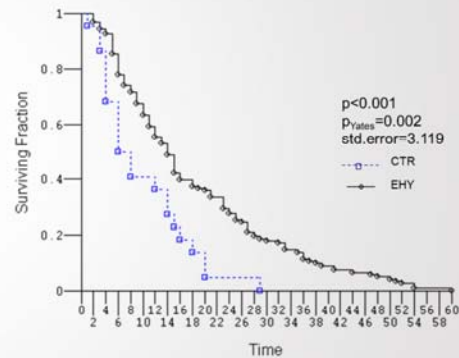
Study 2 (Dani et al., 2003): Description

- Retrospective, monocenter, cohort, double-arm study
- Non-small cell lung cancer (N=186) (Szent Barabala Hospital, Tatabánya):
 - Study arm (SA), standard treatment + oncothermia (n=147)
 - Control arm (CA), standard treatment only (n=39)
- Recruitment period: 1998 - 2001
- Average age: SA=57 yrs, CA=57.3 yrs
- Gender structure: SA=67.8% males, CA=79.2% males
- Metastatic cancer at Dx: SA=59%, CA=45%
- Metastatic cancer at 1st EHY: 88%
- Oncothermia included in the complex treatment

Study 2 (Dani et al., 2003): Survival

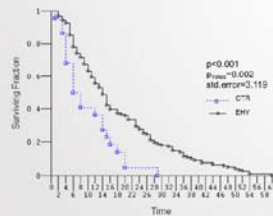
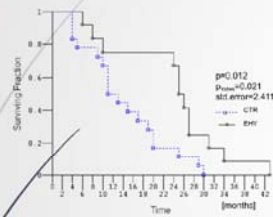


Stage IIIA (n=31/14)



Stage IIIB-IV (n=87/18)

Study 2 (Dani et al., 2003): Survival



Year	1	2	3	4	5	MST
OS (EHY)	58,0%	28,0%	12,0%	5,0%	1,0%	15
OS (Control)	36,0%	4,0%	0,0%	0,0%	0,0%	13.8

Since Dx	Study arm (EHY+)		Control arm (no EHY)	
	Absolute	Disc*	Absolute	Disc*
LY/pat	1,04	1,02	0,4	0,4
QALY**/pat	0,68	0,67	0,26	0,26

* 3% annual discount rate

** Average HRQoL throughout ST: SA=0,65, CA=0.55

Study 3 (Parmar, 2015)

- Retrospective, monocenter, cohort, single arm study
- Integrated Health Clinic (Fort Langley, BC, Canada)
- Non-small cell lung cancer stage IV (N=30)
- Recruitment period: Aug 2010 - Jun 2015
- Stage IV at Dx: 100%
- Oncothermia included in the complex treatment
- Oncothermia applied in the III quartile of survival time

Year	1	2	3	4	5
OS	64,8%	33,5%	33,5%	26,8%	13,4%

Since Dx	Absolute	Discounted*
LY/patient	1,72	1,65
QALY**/patient	1,12	1,07

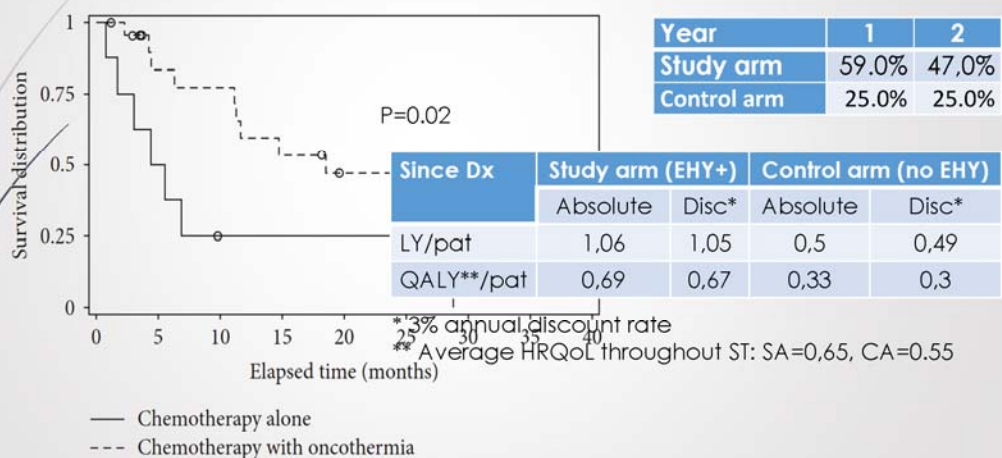
* 3% annual discount rate

** Average HRQoL throughout ST =0,65

Study 4 (Lee, 2011): Description

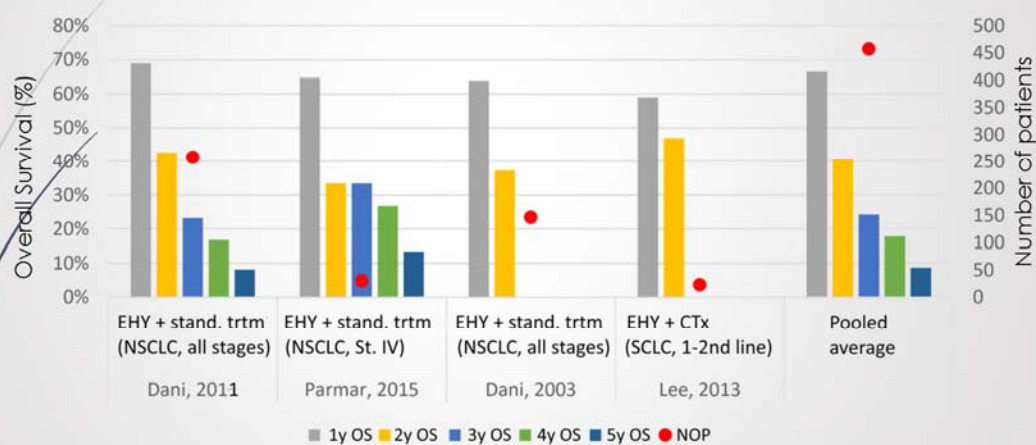
- Prospective, monocenter, cohort, double-arm study
- Gangnam Severance Hospital, Yonsei University, Korea
- Small cell lung cancer (N=31):
 - Study arm (SA), chemotherapy + oncothermia (n=23)
 - Control arm (CA), chemotherapy only (n=8)
- Recruitment period: ongoing study
- Oncothermia in combination with chemotherapy in 1st-2nd line treatment of SCLC.

Study 4 (Lee, 2011): Survival



Synthesis of Evidences

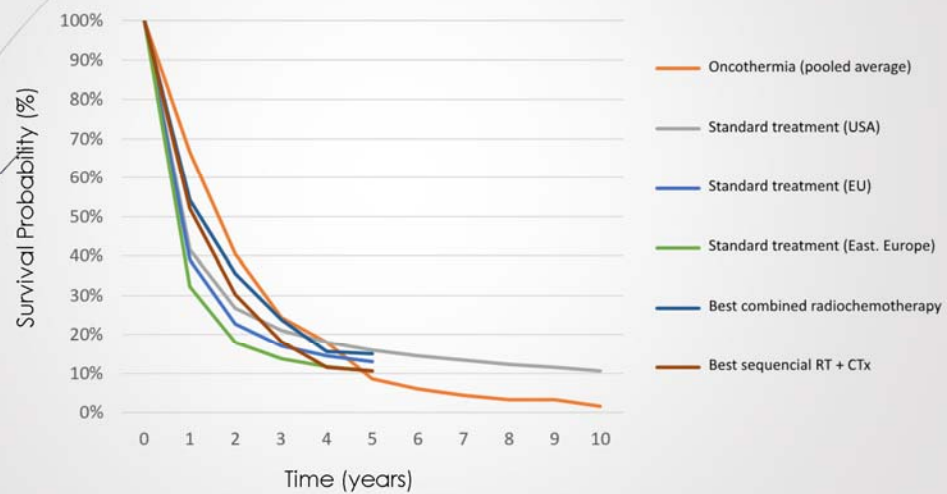
Synthesis of Survival Data



Comparison of Overall Survival

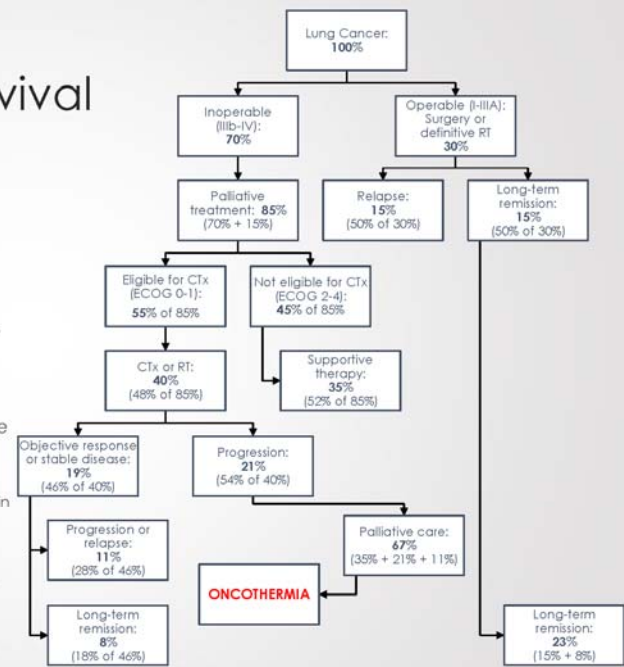
Dataset	1	2	3	4	5
Oncothermia (pooled average)	66,6%	40,6%	24,3%	17,9%	8,7%
Standard treatment USA (SEER)	41,6%	26,8%	21,0%	17,9%	15,9%
Standard treatment EU (Eurocare-5)	39,0%	22,7%	17,1%	14,5%	13,0%
Standard treatment East. Europe (Eurocare-5)	32,4%	18,0%	13,7%	11,7%	10,6%
Best radiochemotherapy	54,2%	35,6%	23,8%	15,6%	15,1%

Comparison of Overall Survival



Why long-term survival drops down?

- Currently oncothermia is applied as a 3rd-4th line treatment after fail of the previous treatment, or if other treatment is impossible.
- As such oncothermia sample consists of the patients with poor prognosis:
 - Low performance status (ECOG 2-4) not eligible for CTx and RT;
 - CTX and RT resistant patients;
 - Patients with relapse or progression.
- Oncothermia is used in 3rd quartile of ST, where chances for success significantly lower.
- Effect of basis:
 - Treatment results in USA are 10-20% better than in EU
 - Treatment results in Hungary are 10-20% worse than in EU
 - The main trials were performed in Hungary from 1997 to 2002 (before entrance to EU in 2004), when the treatment quality was even lower.

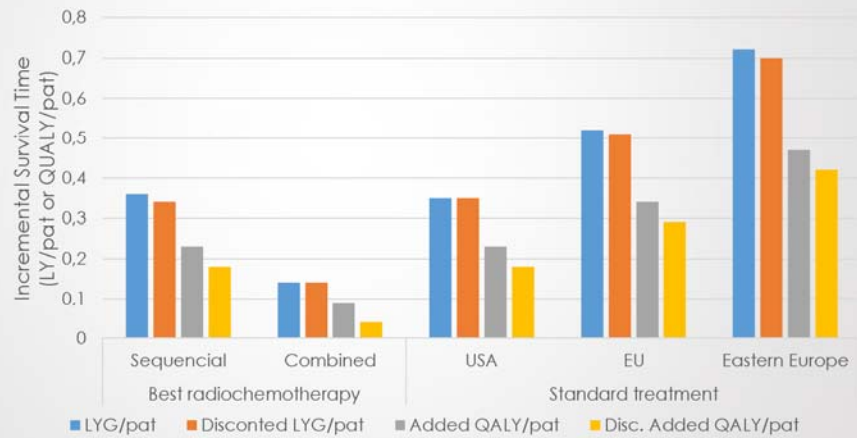


Incremental Utility of Oncothermia

	Best radiochemotherapy		Standard treatment		
	Sequencial	Combined	USA	EU	Eastern Europe
LYG/pat	0,36	0,14	0,35	0,52	0,72
Disconted LYG/pat	0,34	0,14	0,35	0,51	0,70
Added QALY/pat	0,23	0,09	0,23	0,34	0,47
Disc. Added QALY/pat	0,18	0,04	0,18	0,29	0,42

- Oncothermia provides increment of utility versus all comparators.
- The lesser increment is versus best combined chemoradiotherapy (0,04 QALY/pat)
- The maximal increment is versus Eastern European standard treatment (0,42 QALY/pat)

Incremental Utility of Oncothermia



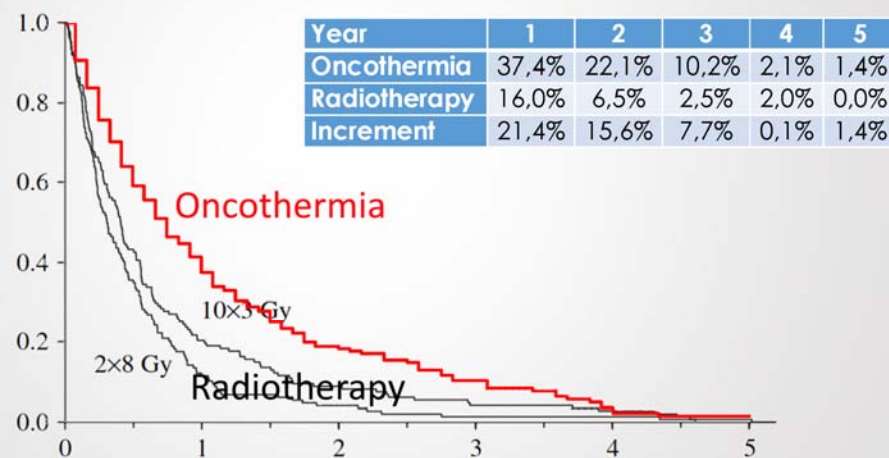
Cost-Utility Analysis

Cost-Utility Analysis of Oncothermia versus Radiotherapy in Treatment of Lung Cancer

Oncothermia vs Radiotherapy: Comparison of cohorts

	Oncothermia	Radiotherapy
Clinical Trial	Dani, 2011	van den Hout, 2006
Country	Hungary	Netherlands
Recruitment	1997-2003	2000-2003
Number of patients	258	297
Average age	57.4	69
Males	68%	80%
Stage IV	80%	47%
Treatment line	3 rd -4 th	1st
Time to treatment	11.9 months	1 month
Pre-treatment	2.69 courses/pat	0.2 courses/pat

Oncothermia vs Radiotherapy: Comparison of Survival



Oncothermia vs Radiotherapy: Economic Assessment

- Life discounting 3%/year.
- Monetary discounting not used.
- Radiotherapy HRQoL=0.57.
- Though oncothermia always improves life quality versus radiotherapy, the equal HRQoL=0.57 was used for both trials.
- Radiotherapy costs = 3,869 \$ /pat.
- Oncothermia costs = 1,727 \$/pat:
 - Cost of 1 session EUR 140 (exchange rate 2005 = 1,4 \$/EUR).
 - Direct non-medical costs calculated proportionally to radiotherapy costs.

Oncothermia vs Radiotherapy: Cost-Utility Analysis

	QALY/pat	\$/pat	CER (\$/QALY)
Oncothermia	0.408	1,727	4,230
Radiotherapy	0.151	3,869	25,619
Increment (OT – RT)	0.257	-2,142	-8,328

■ ICER = - 8,328 \$/QALY

- This means that radiotherapy generates \$8,238 extra costs per each QALY compared to oncothermia use.

Sensitivity Analysis

- Radiotherapy costs:
 - Average: 8,081 \$/pat
 - Median: 8,609 \$/pat
 - Minimum: 3,874 \$/pat
 - Maximum: 14,491 \$/pat
- Oncothermia costs:
 - Minimum: 1,283 \$/pat
 - Average: 1,727 \$/pat
 - Maximum: 3,095 \$/pat (300 EUR/session)
- **ICER = -3,008 — -51,342 \$/QALY**
- **Radiotherapy instead of oncothermia generates \$3,000 — \$50,000 of extra costs per QALY.**

Year	Country	\$/pat
2003	Canada	9 060
2005	Netherlands	3 874
1999	Canada	4 086
1999	Canada	5 673
2012	Netherlands	8 291
2012	Netherlands	8 609
2012	Netherlands	9 143
2012	Netherlands	9 503
2012	Netherlands	14 491
	Average	8 081
	Median	8 609
	Minimum	3 874
	Maximum	14 491

Cost-Utility Analysis

Cost-Utility Analysis of Oncothermia versus
Chemotherapy in Treatment of Lung Cancer

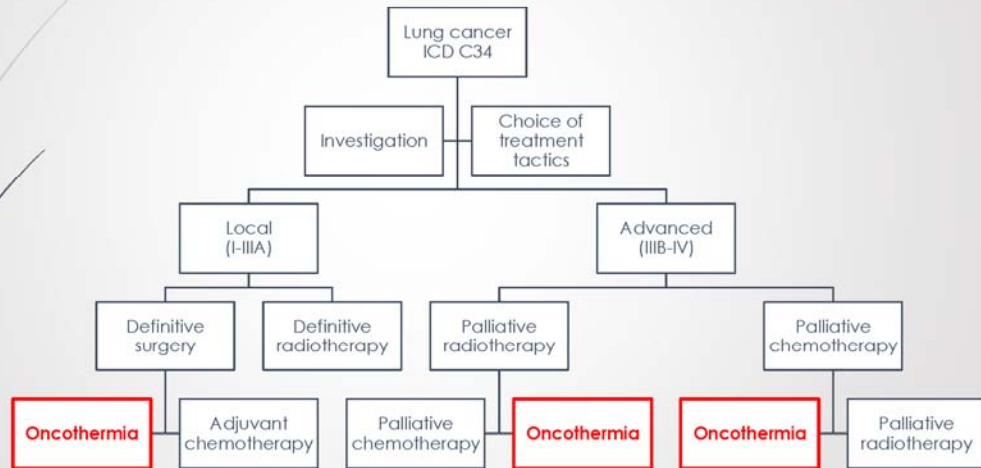
Oncothermia vs Chemotherapy

- Oncothermia of 3rd-4th line versus 1st line Chemotherapy
- Platinum-based Chemotherapy adds 0,49-0,63 LY/pat (average 0,585).
- Chemotherapy costs 5,932-202,176 \$/QALY (average 42,841 \$/QALY)
- ICER = -10,825 — -250,000 \$/QALY
- **Chemotherapy instead of oncothermia generates >\$10,000 of extra costs per QALY.**

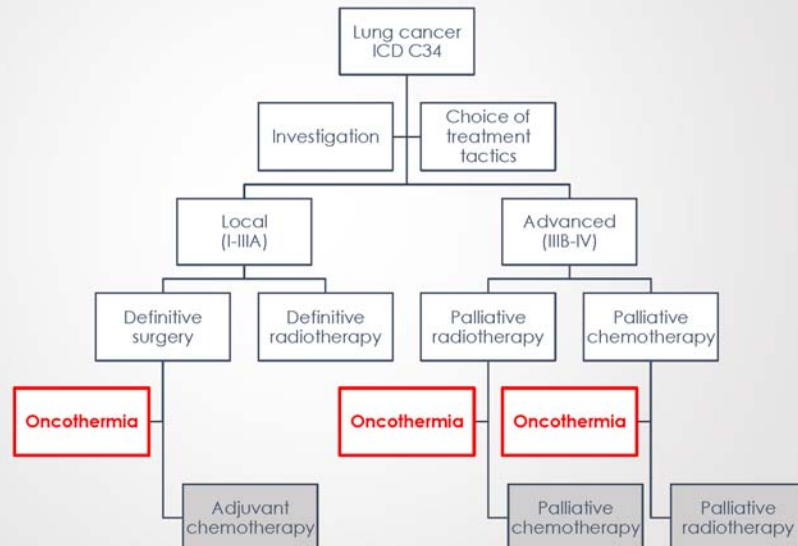
Chemo	Year	\$/unit	Unit	Added units
DOC	2010	48 978	QALY	
DOC	2001	98 493	LY	0,500
DOC	2003	22 181	LY	
DOC	2001	20 654	LY	
DOC (2nd line)	2001	25 442	LY	0,490
DOC средняя		42 412	LY/QALY	
ERL	2014	89 129	QALY	
ERL	2007	202 178	QALY	
ERL	2007	88 030	LY	
ERL	2009	75 710	LY	
ERL	2011	36 838	LY	
ERL average		98 377	LY/QALY	
GEF	2014	56 049	QALY	
GEM	2001	8 251	LY	0,580
GEM	2006	16 603	QALY	
GEM	2002	7 581	PFLY	
GEM+CARB	2014	37 030	QALY	
GEM+CIS	2001	14 559	LY	0,730
GEM+CIS	2014	49 789	QALY	
GEM average		27 123	Pass.	
PAX	2001	43 071	LY	0,540
PAX	2001	67 585	LY	0,540
PAX (135) +CIS	2001	12 379	LY	0,780
PAX (175) +CIS	2001	20 480	LY	0,730
PAX (250) +CIS	2001	17 551	LY	0,830
PAX average		32 213	LY	
FEM	2010	61 470	QALY	
FEM+CIS	2012	56 000	QALY	
FEM average		58 735	QALY	
VIN+CIS	2006	16 603	QALY	
VNB	2001	5 932	LY	0,590
VNB+CIS	2001	7 549	LY	0,700
VNB+CIS	2014	59 797	QALY	
VNB average		24 426	LYS	
CTx average		42 841		0,585
CTx minimum		5 932		0,490
CTx maximum		202 178		0,626

Budget Impact Analysis

Budget Impact Analysis: Model 1



Budget Impact Analysis: Model 2



Budget Impact Analysis: Model 2 Pre-requisites

- Utility of conventional chemoradiotherapy cancer treatments averages 0.4 QALY/pat (0.3-0.85 QALY/pat)
- Oncothermia in complex treatment provides the same of higher utility (0.4-1.0 QALY/pat)
- Thus, oncothermia provides enough enhancement of any method from bimodal intervention to substitute the other one.
- Therefore, oncothermia can substitute chemotherapy OR radiotherapy in bimodal intervention.

Budget Impact Analysis: Model 2 Pre-requisites

- Radiotherapy alone is modestly effective in lung cancer treatment but its effect is strongly potentiated by platinum-based chemotherapy.
- At the same time, concurrent chemotherapy increases toxicity of radiotherapy, namely radiation induced lung injury (radiation pneumonitis) and radiation esophagitis.
- With total dose >40 Gy and concurrent chemotherapy, the both radiation-induced lung and esophagus injury are almost inevitable (100%).
- The substitution of chemotherapy by oncothermia can reduce the toxicity and increase survival.

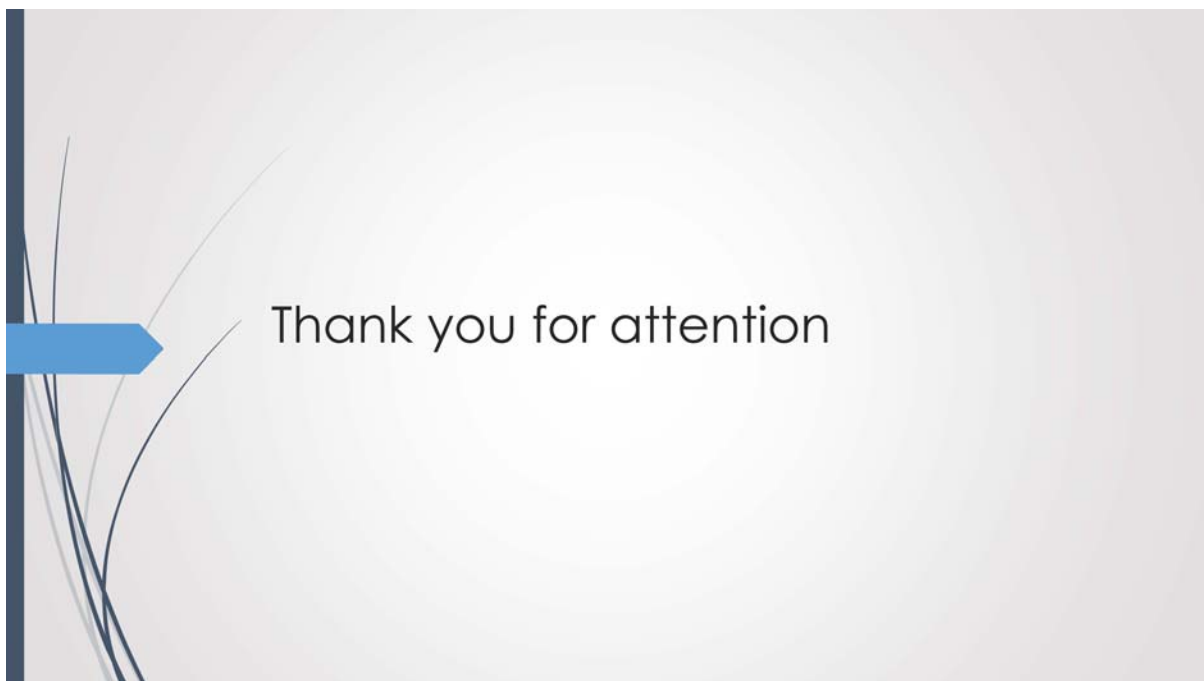
Budget Impact Analysis: Model 2 Pre-requisites

The results of the trial (2012) performed in radiation oncology center of Research Institute named after academician Meshalkin in Novosibirsk (Russia):

- 38 patients with non-small cell lung cancer (all stages) were treated in 2010 by 3D-conformal radiotherapy (total dose 64.25 Gy (equivalent dose 70-76 Gy), single dose 2.75 Gy 5 x week) in combination with oncothermia (10 sessions, 3 x week, 150W x 90 min).
- Beneficial response 95%, including objective response (CR + PR) in 53% and stable disease in 42%; 5% of progression.
- **1-year survival – 97.4%!**

Results

- Oncothermia in the 3rd-4th line complex treatment of lung cancer provided better 1-3 year survival compared to any 1st line conventional treatment except of surgery, including the best chemoradiation treatment.
- Oncothermia provided virtually the same utility as the best concurred chemoradiation treatment (+0,04 QALY/pat) and the better utility than standard treatment in USA and Europe (+0,42 QALY/pat versus Eastern Europe).
- Oncothermia showed the better cost-utility compared to radiation therapy with ICER = -3,000 — -50,000 \$/QALY.
- Oncothermia showed the better cost-utility compared to chemotherapy with ICER = -10,000 — -250,000 \$/QALY.
- Thus, oncothermia is pharmacoeconomically preferable treatment versus either radiotherapy or chemotherapy in complex treatment of lung cancer.



Hyperthermia combined with radiation in cervical cancer

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² iThemba LABS, National Research Foundation, South Africa

³ Department of Basic Medical Sciences, Ghent University, Belgium

HYPERTHERMIA COMBINED WITH RADIATION IN CERVICAL CANCER

C.A. Minnaar¹; J.A. Kotzen¹; A. Baeyens^{1 2 3}

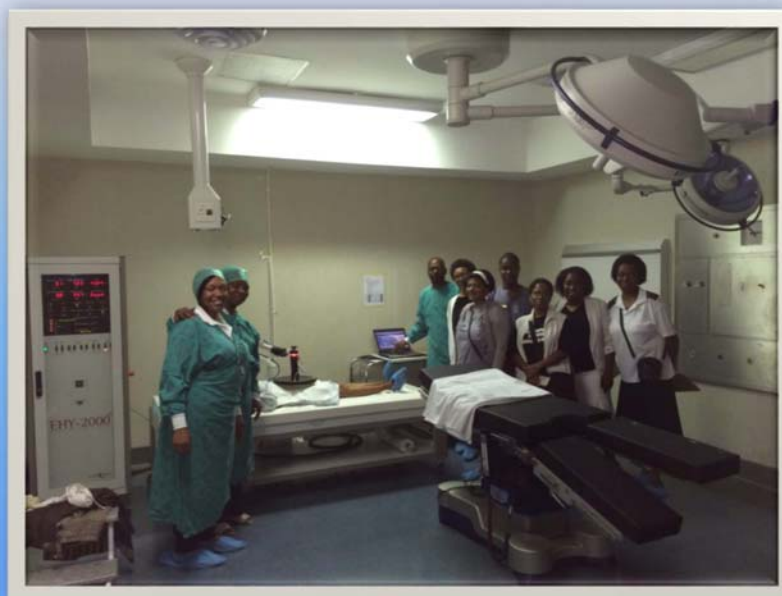
¹ *Department of Radiation Sciences, Wits University, South Africa*

² *iThemba LABS, National Research Foundation, South Africa*

³ *Department of Basic Medical Sciences, Ghent University, Belgium*

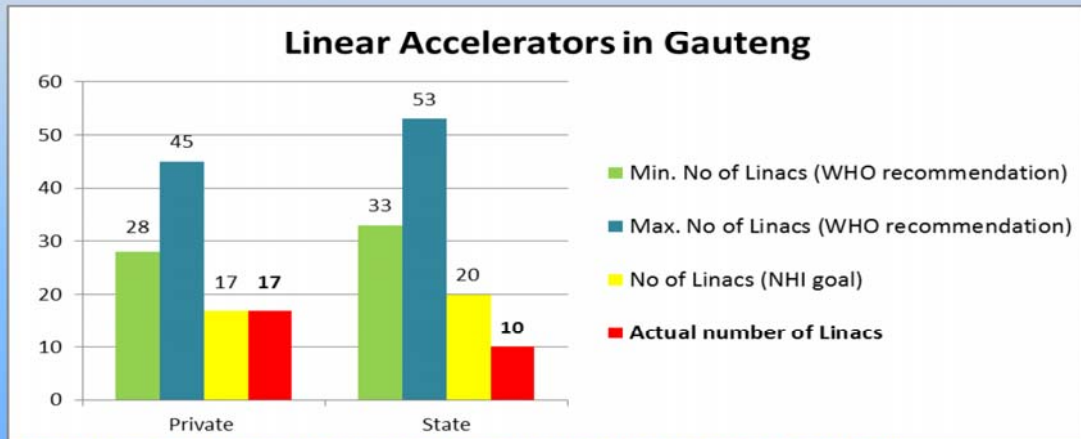


South Africa



South Africa

- Limited resources



46% of the population make use of private healthcare (stats SA 2011).

Gauteng is in urgent need of an additional linear accelerator that can serve both private and state patients.

South Africa

- Limited resources
 - Not enough Linacs
 - PET and CT machines were not working for 6 months
- Poverty
 - Transport problems
 - Missed appointments
 - Lost to follow ups
- Patients present at advanced stage of disease
- Immunocompromised
 - Can't use Cisplatin as a radiosensitiser

Can we help overcome the challenges of third world healthcare?



Aim

To determine the clinical effects of the addition of modulated electro-hyperthermia to the standard treatment protocols LACC patients.

OUTCOMES:

- Local disease control at 6 months (PET scan)
- 2 year Survival
- Toxicity: early and late
- Quality of Life



Materials and Methods

Sample group

- N=236 (current n=174 enrolled)
- Public Healthcare patients
- **Ages** 18-70 years
- **FIGO staging:** IIB– IIIB squamous cell
- **Comorbidities:** Diabetes and hypertension
- **Excluded:** Contraindications to treatment
Immunocompromised patients
Renal dysfunction



Materials and Methods

Treatment protocol

- **External Beam Radiotherapy (EBRT):**
50 Gy over 25 fractions
- **Brachytherapy:** High Dose Rate (Ir^{192})
3 x 8 Gy doses
- **Cisplatin:** 1- 2 doses 80mg/m²

EHT Protocol: 2 x 55 min Rx/week



Materials and Methods

Adverse Events

- * **Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

43 symptoms were graded and grouped into: *Haematological Ototoxicity, Neurotoxicity, Immunological, Rectal, Digestive, Dermatological, Urinary, Renal, Gynaecological*

- * **Time Points:**

- * **Acute Toxicity:** Weekly during treatment
6 weeks post treatment
3 months post treatment
- * **Late Toxicity:** Every 6 months post treatment

Materials and Methods



Quality of Life

- EORTC (CX 30) and cervix specific (CX24)
- EuroQoL (EQ-5D-5L)
- **Time points:**
 - Pre treatment
 - 6 weeks post treatment
 - 3, 6, 12, 18, 24, months post treatment



Results



First 100 patients:

Screening failure: 27%

Death

Development of contraindications or co-morbidities before or during treatment

Moved to palliative care after PET scan

Decided against treatment

HIV + : 52% HIV - : 48%

Results



FIGO STAGE distribution

Excluding Screening failures

FIGO STAGE	HT						no HT					
	HIV+ 12	HIV- 14	Total 26				HIV+ 26	HIV- 21	Total 47			
	n %	n %	n %				n %	n %	n %			
Stage IIB	4 33%	4 29%	8 31%				9 35%	3 14%	12 26%			
Stage IIIA	0 0%	0 29%	0 0%				0 0%	1 5%	1 2%			
Stage IIIB	8 67%	10 29%	18 69%				17 65%	17 81%	34 72%			

Results



AGE distribution

Excluding Screening failures

AGE	HT						no HT					
	HIV+ 12	HIV- 14	Total 26				HIV+ 26	HIV- 21	Total 47			
	n %	n %	n %				n %	n %	n %			
<30	0 0%	0 0%	0 0%				2 8%	0 0%	2 4%			
30-50	7 58%	5 36%	12 46%				16 62%	4 19%	20 43%			
>50	5 42%	9 64%	14 54%				8 31%	17 81%	25 53%			

Results

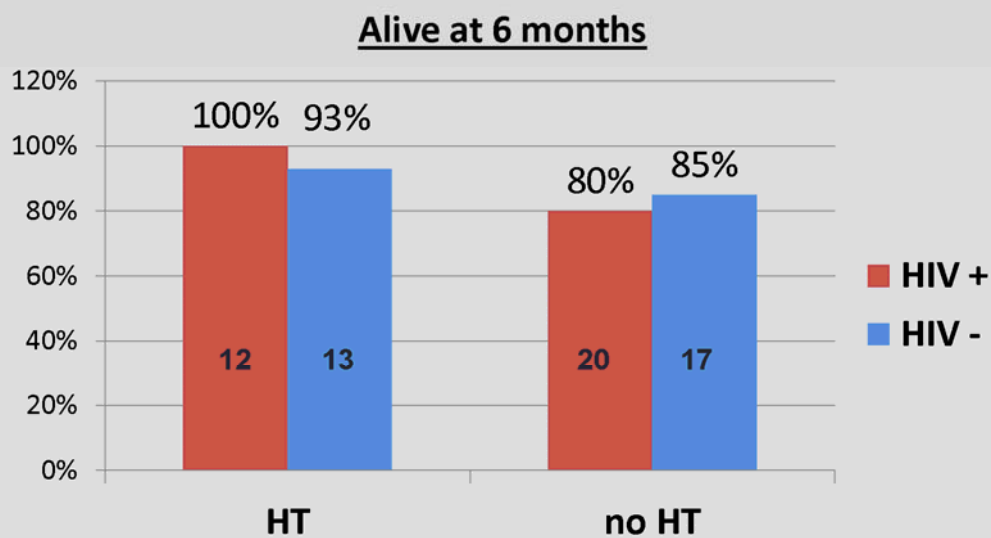


6 month survival

Excluding non disease related deaths, n=71

6 months	HT						no HT					
	HIV+ 12	HIV- 14		Total 26	HIV+ 25		HIV- 20	Total 45				
	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	n %	
Alive	12 100%	13 93%	25 96%	20 80%	17 85%	37 82%						
Deceased	0 0%	1 7%	1 4%	5 20%	3 15%	8 18%						

Results: 6 month survival



Results



6 month Local Disease Control

70 patients completed 6 month PET scan

1 patient was unable to lie still due to bone pain

	Total n	26 %	Total n	44 %
1. Complete response	13	50%	17	39%
2. Partial response	10	38%	10	23%
3. No change	2	8%	2	5%
4. Local progression	0	0%	7	16%
5. Death d/t disease	1	4%	8	18%

Frequency table, expected frequency, chi2 contribution

Fisher's exact = 0.058

Results: Quality of Life



Analysis of change from baseline score

(more than 30 points < or >)

And score at specific time points

AT INITIATION:

Worse in EHT group:

Better in EHT group:

Sexual worry, nausea,

role functioning

■ Results: Quality of Life

At 6 Weeks

Nausea and vomiting ↑ HT group ($p=0.0109$)

At 3 Months

Pain ↑ in HT group ($p=0.007$)

Appetite ↑ in HT group ($p=0.0221$)



At 6 Months

Sexual worry ↑ in HT group ($p=0.0197$)

Emotional functioning ↑ in HT group ($p=0.0307$)

Factors which may affect toxicity:

- **HIV status:** *No significant effect*



- **Hyperthermia (HT):** *Significant effect in:*

On treatment and 6 weeks post treatment

Diarrhoea: ↑ Frequency of **Grade I** in HT

Urinary pain: ↑ Frequency of **Grade II** in non HT

Cystitis: ↑ Frequency of **Grade II** in HT
at 3 months only



Discussion



- Positive trend in the six month survival
- Positive trend in local disease control
- Difference in Quality of Life and Acute toxicity is not significant
- Late side effects will be assessed with continued follow up.
- Overall survival will be followed up

Conclusion



- Initial results are promising with therapeutic benefit.
- Continued follow up and increased patient numbers needed to strengthen the results.



THANK YOU

Carrie Strauss
Ans Baeyens
Jeffrey Kotzen

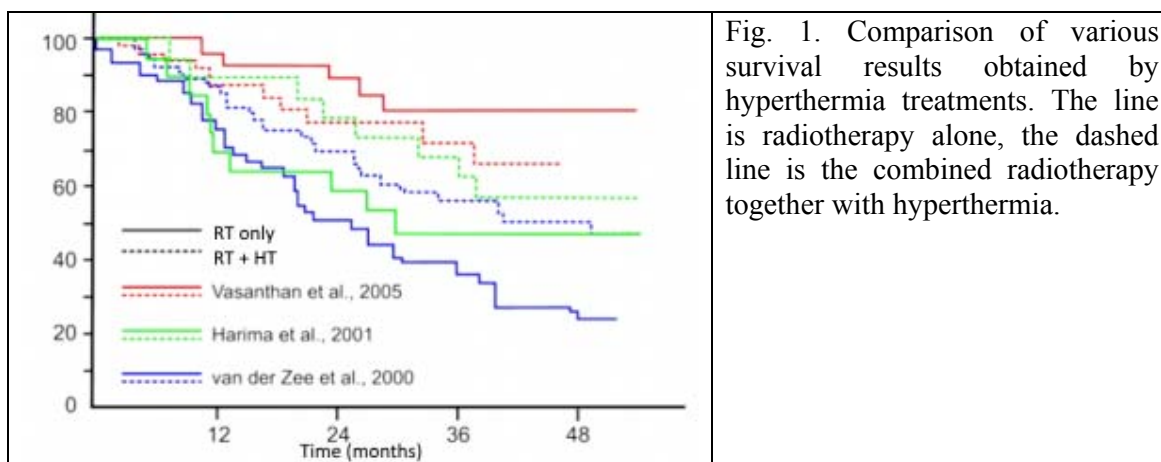


Comment to C.A. Minnaar's results
Sergey V. Roussakow*

* Galenic Research Institute, Moscow, Russia

The quality of the study design is an important issue. Per my view, the applied full protocol of radiotherapy by high-brachytherapy, with dose 74 Gy and increased cisplatin - in principle, is the best international protocol for cervix carcinoma. In this study, made by Dr. C. Minnaar, Oncothermia shows significantly better local control after evaluating 100 patients (42%). Differences in survival rates approaching the level of confidence is already at 6 months (when the differences are usually minimal), and an advantage in the quality of life is definitely significant (0.7-3% chance of error). The results are quite remarkable, especially considering the factor of proper control.

In previous hyperthermia studies for advanced cervix cancer of van der Zee (2000) and Harima (2001), the radiotherapy dose was less than 60 Gy. Accordingly, no significant differences were shown against control, whereas in comparison with the proper therapy (dose > 70 Gy) results in bimodal thermo-radio-therapy in Harima's and van der Zee's research were worse. The international multicenter study Vasanthan (2005) revealed these problems. Vasanthan's study used an adequate radiotherapy (72 Gy, but without amplification) and the most effective hyperthermia (average temperature in 41.8°C in the tumors, while it was 40-41°C in the study of van der Zee). Vasanthan's result was negative: hyperthermia worsened survival and in group IIB deterioration was significant. At the same time, the control of the RT group Vasanthan's research showed remarkable results: 4-year survival rate was 80%, which significantly exceeded the results of Harima and van der Zee, and it reliably and exceeded the results of RT-controls (50% and from 28% Harima in van der Zee), Fig. 1.



Given the distortions, no study on hyperthermia radio-modification in cervical cancer, of course, can be considered successful.

Thus, the South-African study by Dr. Minnaar's onco-thermo-radio-therapy has all chances to become the first in the history of successful research on physical radio-modification in locally advanced cervical cancer.

The newest study of the van der Zee group (Lutgens LCHW et al, 2016) shows no difference between the bimodal radiotherapy + cisplatin and radiotherapy + hyperthermia. The event-free survival is shown on Fig. 2.

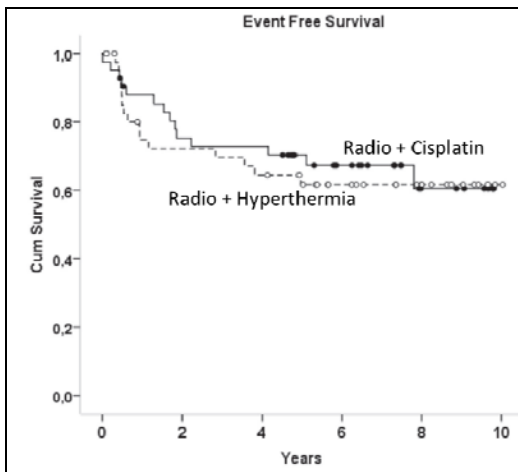


Fig. 2. The event free survival in the latest result of hconventional hyperthermia study for locally advanced cervix carcinoma. (From Lutrens LCHW et al 2016).

The complete comparison of the cervix results is shown on Fig. 3. The new radiotherapy plus hyperthermia results has remarkable correspondence with the same type of treatment earlier by Vasanthan et al.

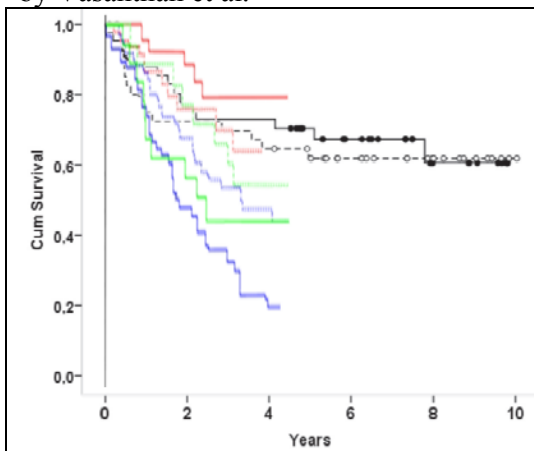


Fig. 3. Comparison of various survival results obtained by hyperthermia treatments. The line is radiotherapy alone and with cisplatin in case of black line, and the dashed line is the combined radiotherapy together with hyperthermia. The black patterns are from (Lutrens LCHW et al 2016), the others are equivalent with Fig. 1.

Noteworthy characteristic pattern of oncothermia effect is its definite difference from conventional hyperthermia. In all the conventional hyperthermia researches it shows the gain of complete remission, in some cases, the survival time does not increase parallel, but oppositely it decreases with growing local control. Oncothermia complete remission usually shows parallel gain of local control survival time and quality of life as well.

van der Zee J, González González D, van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. *Dutch Deep Hyperthermia Group. Lancet.* 2000; 355 (9210): 1119-25.

Harima Y, Nagata K, Harima K, et al. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *Int J Hyperthermia.* 2001; 17 (2): 97-105.

Vasanthan A, Mitsumori M, Park JH, Zhi-Fan Z, Yu-Bin Z, Oliynychenko P, Tatsuzaki H, Tanaka Y, Hiraoka M. Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the international atomic energy agency. *Int J Radiat Oncol Biol Phys.* 2005; 61 (1): 145-53.

Ludy C.H.W. Lutgens, Peter C.M. Koper, Jan J. Jobsen, et al. Radiation therapy combined with hyperthermia versus cisplatin for locally advanced cervical cancer: Results of the randomized RADCHOC trial. *Radiotherapy and Oncology.* 2016; 120(3):378-382.

Pakistan has highest breast cancer rate among Asian countries

Adeel Ahmed*, Sara Shafi**

* Oncothermia Clinics, Karachi

** The Lyceum School, Karachi

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‘Pakistan has highest breast cancer rate among Asian countries’

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November 06, 2016

Print: [Karachi](#)

Pakistan has the highest breast cancer rate among Asian countries. Young women also have been diagnosed with advanced stage of breast cancer. In rural areas, women are also developing breast cancers every year because it is an inherited disease, which transmits from mother to daughter.

These views were expressed by Adeel Ahmed, Manager Marketing and Administration at the Oncothermia Clinics, during an awareness programme about breast cancer at the Lyceum school, held on Thursday. The programme was arranged by Sara Shafi, student of A-Level at The Lyceum School.

According to her, the initiative to arrange the programme regarding breast cancer awareness was to target young women, school teachers, staff and students in collaboration with the Oncothermia Clinics, using the latest state-of-the-art technique to treat different types of cancers. “The goal of this awareness programme is to educate about breast cancers, its causes and consequences, early detection and screening tests, risk factors, and prevention strategies.”

Adeel Ahmed said breast cancer was on the rise among young women, including unmarried girls in Pakistan, and alarmingly women in early 40s were being diagnosed with this lethal disease, unlike the rest of the world where the onset of the disease is usually seen in the mid to late 60s.

He added there were many misconceptions attached to breast cancer among women including many wrong concepts and believes that breast cancer was contagious. “Of all the breast cancer cases diagnosed in Pakistan, around 12 to 19 percent cases are of unmarried girls. Prolonged use of estrogens like oral pills for birth control can also trigger the risk of breast cancer in next generation of such woman. Woman delivering first baby after age of 30 years also have increased risk of breast cancer.”

For diagnosis of disease at very early stage, every girl after puberty should do self-examination, and if any lump is found, she should immediately consult any specialist for check-up and screening, he added. “Every woman after age of 40 years should get her screened for breast cancer once a year.”

**Bestmögliche Ergebnisse der Oncothermia
(Elektrohyperthermie) bei der Therapie von Karzinomen
und Sarkomen in Kombination**

Brockmann W.P.*

* Institut OncoLight®, Hamburg

Extended research to earlier publication

Bestmögliche Ergebnisse der Oncotherapie (= Elektrohypothermie) bei der Therapie von Karzinomen und Sarkomen in Kombination mit weiteren schulmedizinischen Behandlungsmethoden - ohne wesentliche Nebenwirkungen

Brockmann, W.P., Institut OncoLight®-Hamburg

Teil A

Die Oncotherapie in sehr gut verträglichen lokalen, lokoregionären und systemischen Therapiekombinationen

Nicht „am Leben vorbei überleben“ zu müssen, sondern Lebensqualität praktisch uneingeschränkt auch während einer erfolgreichen Krebstherapie samt nachfolgender Remission genießen zu können, ist zu einem wesentlichen und immer häufiger erreichbaren Ziel der Elektrohypothermie bzw. Oncotherapie geworden.

Über dieses Ziel hinaus bleibt jedoch ohne zusätzliche Behandlungsmaßnahmen schon die erstrebte Remission in der überwiegenden Mehrzahl der Fälle pure Illusion. Ein bloßes Hinhalten der Erkrankung über ein paar Monate ohne sichtliche Verkleinerung von Tumor oder Metastasen im Zielvolumen und ohne wesentlichen Rückgang erhöhter Serumentumormarker darf dem behandelnden Arzt nicht mehr genügen. Seine Aufgabe muss die Einbindung der EHT in ein logistisch anspruchsvolles Gesamtkonzept sein, das evtl. weniger in die Hand des vorrangig systemisch arbeitenden Medizinischen Onkologen und Hämatologen oder kurz: Pharmakoonkologen gehört, als zur Therapie des gezielt einen „Ort der Not“ behandelnden Radioonkologen, dem im Sinne einer Therapiekombination auch der Begriff der Chemoradiotherapie hierfür seit Jahren nicht mehr fremd sein muss.

Dabei erlaubt die Kombination aus einstündiger lokaler oder lokoregionärer Tiefen-**Elektrohypothermie** (= EHT) und chemotherapeutischen sowie radioonkologischen Maßnahmen, jedes dieser zusätzlichen Verfahren in teilweise deutlich verringerter Dosis anzuwenden - gleichgültig, ob allein oder gemeinsam hinzugefügt - so dass man bei eindeutig verbesserter Wirkung immer noch ohne lästige oder gar belastende Nebenwirkungen auskommen kann.

In aller Regel gehören zu einer solchen *OncoLight-Therapie®* je nach Primärtumorhisto-

logie als lokal im Zielvolumen sensibilisierende Lowdose-**Chemotherapie** (= LDCT) jeweils mehrfach applizierte, geringe Mengen Mitomycin (zwischen 3,5 und 7 mg Absolutdosis als Bolus i.v.), Carboplatin (zwischen 40 und 70 mg Absolutdosis in 5%-iger Glucoselösung als i.v.-Infusion über ca. 30 Min.) oder z.B. Gemcitabine (bis zu 750 mg Absolutdosis in 250 ml NaCl-Lösung als 1-Std. i.v.-Infusion unter 8 mg Prednisolonschutz der Lunge gegen Pneumonitiden mit Fibrosen). Bei Mammakarzinom-Patientinnen können zur EHT u.a. auch über mehrere Wochen hinweg 50 mg Cyclophosphamid oder 50 mg Ixoten pro die per Os hinzugefügt werden.

Die **Strahlentherapie** mit Linearbeschleunigern kommt bei nicht systemischen Problemen ebenfalls als zusätzliche simultane Behandlungsoption regelmäßig zum Einsatz. Als radioonkologische Besonderheit wird sie als akzeleriert-hyperfraktionierte Maßnahme ausgeführt, deren zweimal täglich verabreichte geringe Einzeldosen zwischen 1,1 und 1,5 Gy einerseits das Risiko von Spätnebenwirkungen senken, während die (im Vgl. mit Normfraktionen von 1,8 bis 2,0 Gy) erhöhte Tagesdosis von 2,2 bis 3,0 Gy tumorbiologisch aufgrund der Gesamtbehandlungszeit-Verkürzung eine angestrebte Wirkungsverstärkung zur Folge hat. Dies wird immer dann besonders relevant, wenn anamnestisch schon Dosis-limitierende, hoch dosierte Vorbestrahlungen im Zielvolumen erfolgt sind, oder wenn es sich um Bestrahlungen ganzer Organe handelt wie Lunge(nhälften), Leber und/ oder Gehirn und Rückenmark.

Im Falle größerer Lungenvolumina innerhalb des Bestrahlungsvolumens - z.B. auch bei Mediastinalbestrahlungen - sind Mitomycin und Gemzar wegen des dann potenzierten Risikos von Strahlenpneumonitiden mit konsekutiven Lungenfibrosen streng kontraindiziert. Auch bei Mediastinalbestrahlungen sollte man wegen der Streustrahlung im Lungengewebe

diese beiden Medikamente evtl. gegen Carboplatin einwechseln.

Ansonsten ist auf Allergien (aus eigener Erfahrung heraus bei Carboplatin ebenso wie bei Mitomycin) zu achten und auf das Differenzialblutbild und dabei insbesondere auf die Anzahl der Lymphozyten, um Defizite in der zellulären Immunabwehr zeitig zu erfassen und gegensteuern zu können - insbesondere, wenn noch systemische Immuntherapien, z.B. Impfungen mit Dendritischen Zellen oder Ähnliches, in Frage kämen.

Möchte man unbedingt höhere Temperaturen als 39 Grad Celsius im Zielvolumen der Elektrophysiothermie erreichen, so bietet sich alle 1-2 Wochen eine zeitlich direkt vorgeschaltete moderate **Ganzkörperhyperthermie** (= GHT) bis maximal 39 Grad Celsius an, auf die dann die EHT ohne Zeitverzug „aufgepfropft“ wird, um kumulativ Temperaturen von mehr als 40 Grad im Zielvolumen zu erzeugen. Diese Hyperthermiekombination zwischen zwei Bestrahlungsapplikationen und eine zusätzliche Mitomycin-Gabe am Anfang der GKH verstärken insgesamt die Wirkung an Tumorzellen nochmals deutlich, jedoch ohne zusätzliche, die Befindlichkeit einschränkende Nebenwirkungen z.B. „Verkochungen von Normalgeweben.

Liegen oberflächliche Tumorformen vor oder gar exulzierende Manifestationen, z.B. bei Hautmetastasierungen in Form eines *cancer en curasse* eines Mammakarzinoms, bietet es sich an, etwaige Infrarotleuchten mit Wasserfilterung des GKH-Gerätes zur **Oberflächenhyperthermie** (= OHT) in die Therapie zu integrieren; dies sollte einerseits im Rahmen der GKH aber auch zusätzlich geschehen und insgesamt 1- bis 2-mal wöchentlich durchgeführt werden. Da das Infrarotlicht bis in ca. 2-3 cm Gewebetiefe wirksam ist, können auf diese Weise auch kleine subkutane Metastasenknotten oder Narbenrezidive (mit)behandelt werden.

Auch wenn die Strahlentherapie in solch ein Gesamtkonzept integriert ist, bleibt diese Kombinationsbehandlung - korrekt ausgeführt - auch subjektiv ohne lästige Nebenwirkungen und damit bestens verträglich.

Da alle o.g. Verfahren nur den „Ort der Not“ kurieren können, ist man im Falle immer häufiger und länger auftretender, so erzielter Organ-Remissionen gezwungen, auch systemisch eine weitere Tumorausbreitung zu verzögern oder am besten ganz zu verhindern - ganz bewusst ohne Schwächung der

zellulären Immunabwehr, am besten unter Ausnutzung einer optimalen oder zuvor optimierten Abwehr.

Hierfür bieten sich als sinnvolle Alternative zu Polychemotherapien und während der letzten drei bis fünf Jahre zunehmend aktuell Formen der Immuntherapie an, z.B. regelmäßig verabreichte GKH-Applikationen zur Vermehrung NK-Zellen, Dendritische Zell-Therapien aus autologen geprimeten oder ungeprimeten Monozyten und ggf. unter besonderer Beachtung der Indikationsstellung auch Komplementärtherapien mit Mistelpräparaten, Thymusextrakten, Enzymtherapien, BK-RiV etc..

Teil B

Therapieergebnisse in Wort und Bild

Die exzellenten klinischen Behandlungsergebnisse spiegeln sich in den nachfolgenden CT-MRT- und Dokumentationen wider, bei einigen Patienten von konformen Verläufen gleichzeitig erhobener Serum-Tumormarkertiter voll bestätigt.

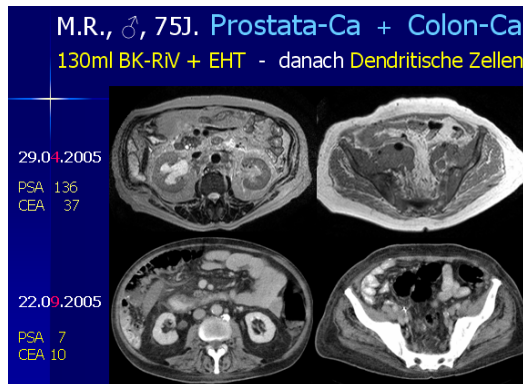
Auf die Güte der Resultate dürfte die Art der Primärhistologie keinen wesentlichen Einfluss haben. Die Verschiedenheit der 10 Primärhistologien bei den im Nachfolgenden vorgestellten 14 Malignompatienten unterstützen diese Annahme.

Prostata- u. Colon-CA
Mammakarzinom
Glioblastoma multiforme IV WHO
Leiomyosarkom
Harnblasen-Ca
Bronchial-Ca (kleinzellig)
Ovarial-Ca
Pankreas-Ca (Adeno-CA)
Gallenwegs-Ca
Lymphangioepitheliales Sarkom

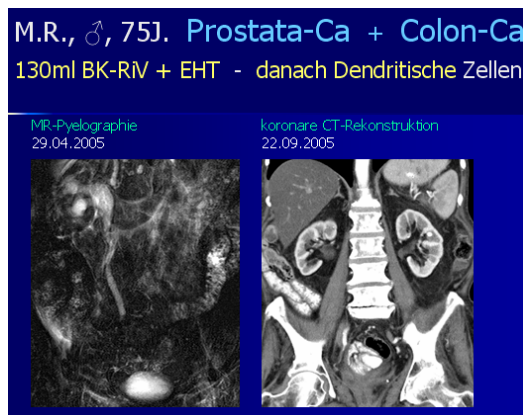
Fall 1 Primärhistologie: Prostatakarzinom

75-jähriger Pat., mit multiplen ossären Metastasen nach knapp einem Jahr freiem Intervall eines fast gleichzeitig aufgetretenen Colon- u. Prostatakarzinoms bei Z.n. Prostatektomie u. Radiatio sowie adjuvanter Colon-Ca-Chemotherapie; ein Jahr lang EHT-Therapie des Skeletts plus insgesamt 135 ml Polypeptid BK-RiV, nach Absetzen des BK-RiV wegen akuter NW infolge simultaner Mistelextraktapplikation fulminanter Tu.-Progress in Leber

und parailiakalen Lymphknoten mit Harnstau re. Daraufhin Wiederaufnahme der EHT (Leber und Becken, großer Applikator, bis 150 Watt Energieaufnahme) plus 5 systemische Dendritische Zell-Immuntherapie-Impfungen → Vollremission im MRT nach 2 Mo. mit weitreichender Remission der Tumormarker (PSA 136 → 7 und CEA 37 → 10), aber Exitus nach 5 Monaten wegen perakuter Lungenembolie, klinisch tumorfrei.



Im April 2005 im Transversalschnitt (MRT, Bild o.li.) Harnstau re., im CT-Bild u.li. nicht mehr erkennbar; Ursache im April (MRT, Bild o.re.) große parailiakale Lymphknotenmetastasenpakete re. (u. li.), Ende Sept. 2005 auf der Aufnahme u.re. nicht mehr eindeutig nachweisbar.



In der rekonstruierten MR-Pyelographie (li. Bild), erkennt man das gestaute NBKS und den erweiterten re. Ureter, in der 2-dimensionalen CT-Rekonstruktion ist auch das re. NBKS wieder normal weit abgebildet.

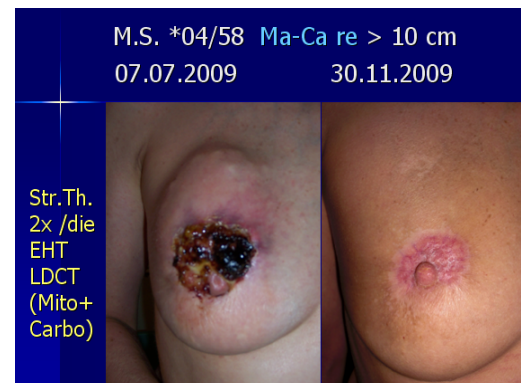
Fall 2 Primärhistologie: Mammakarzinom

1958 geborene Patientin mit Mammakarzinom rechts ohne Standard-Primärtherapie; Tumor seit mind. vier Jahren unter Ablehnung jeder Standardprimärtherapie als langsam progredient von der Pat. selbst getastet. Nach

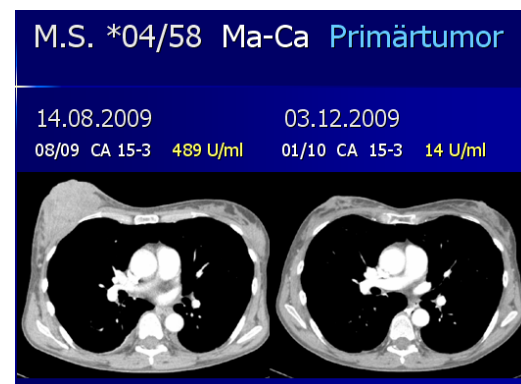
Exulzeration mehrmals auswärtige Galvanotherapie, abgebrochen nach hiesiger Diagnose einer diffusen Lebermetastasierung und Wechsel auf Kombinationstherapie im Bereich von Brust und Achselhöhle rechts sowie unter Einschluss auch der gesamten Leber und einer in den thorakalen Spinalkanal einbrechenden Wirbelkörpermetastase mit Querschnittslähmungsrisiko.

Hyperfraktioniert-akzelerierte Chemoradiotherapie von Mamma und Axilla bis 50,4 Gy GD, ED 1,2 Gy, 2mal täglich sowie beider Leberlappen bis 19,8 Gy GD, ED 1,2 Gy, 2mal /die.

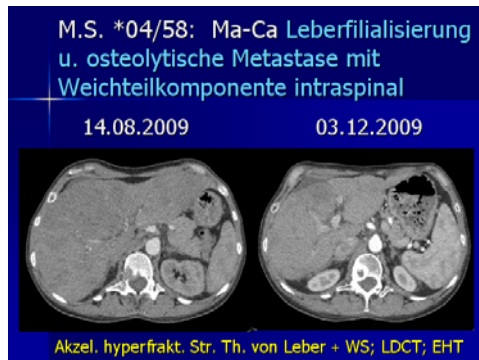
Parallel mehrfach 5-7 mg Mitomycin als i.v.-Bolus und 50mg -Carboplatin-Kurzinfusionen. Keine GKH, Keine OFH. Die synchronen EHT-Applikationen fanden 3mal wöchentlich vor Strahlentherapiebeginn statt, während der Therapie 4mal und nach Therapieende in unregelmäßigen Intervallen 3mal.



Die beiden Fotos zeigen die Abheilung des exulzerierten Primärtumors innerhalb von 3½ Monaten unter o.g. Therapie ohne Auftreten eines späteren Lokalrezidivs bis zum Tod der Patientin 15 Monate nach Therapiebeginn im Leberversagen nach diffus rezidivierender hepatischer Metastasierung bei multilokulärer aber dank Bisphosphonat- und mehrfacher konventioneller bis hypofraktionierter lokaler Strahlentherapie klinisch bedeutungsloser osseärer Metastasierung.



Das linke CT-Schnittbild zeigt den großen Mammatumor vor Therapiebeginn, das rechte das Behandlungsergebnis nach 3½ Monaten. Da die Lebertherapie genauso erfolgreich war (nachfolgende Abbildungen), ist es nachvollziehbar dass sich damit im gleichen Zeitraum auch der entsprechend erhöhte Tumormarker CA 15-3 von 489 U/ml auf 14 U/ml bis in den Normbereich verringern ließ.



Das linke CT-Schnittbild der Leber in der arteriellen Kontrastmittelpase zeigt eine diffuse Vergrößerung der Leber in beiden Lappen und eine scheckig hypodens irreguläre Grundzeichnung als Metastasenleberkorrelat. Gleichzeitig ist der abgebildete Wirbelkörper in der rechten Hälfte dorsal lytisch verändert, wobei die metastatische Läsion schon das Brustmark bedrängt.

Auf dem rechten Bild ist die Leber wieder deutlich kleiner und homogener dargestellt, und die übrigen Abdominalorgane wie Milz und beide Nieren konnten sich wieder kranialwärts zurücklokalisieren. Die Osteolyse zeigt sich ringförmig sklerosiert. Das Querschnittsrisiko war (und blieb) gebannt.

Fall 3 Primärhistologie: Mammakarzinom

61-jährige Patientin mit ausgedehnter exulzierender beidseitig thorakaler Hautmetastasierung eines linksseitigen Mammakarzinoms (Z.n. Ablatio und Nachbestrahlung plus adjuvanter Chemotherapie 2 Jahre zuvor). Täglich hochgradiger Flüssigkeitsverlust durch die offenen Wunden. Seitens der Pat. Ablehnung chemotherapeutischer Maßnahmen.

R.A. *01/48

Ma-Ca Cancer en curasse seit zwei Jahren

OFH, GKH, EHT, LDCT, Radiatio hyperfrakt. akzel. + DC

02.06.2009

03.12.2009



Zweizeitiges Vorgehen betreffs linker und rechter Thoraxseite: erst hyperfraktioniert-akzelerierte Elektronenbestrahlung der linken Thoraxwand, danach der rechten, jeweils bis 45 Gy GD, 1,5 Gy ED, 2mal pro die. Gleichzeitig LDCT mit Mitomycin, und Carboplatin, EHT, GKH und OFH.

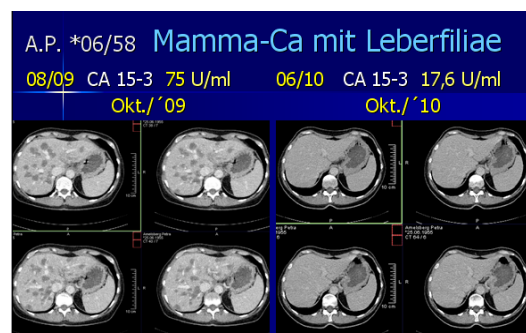
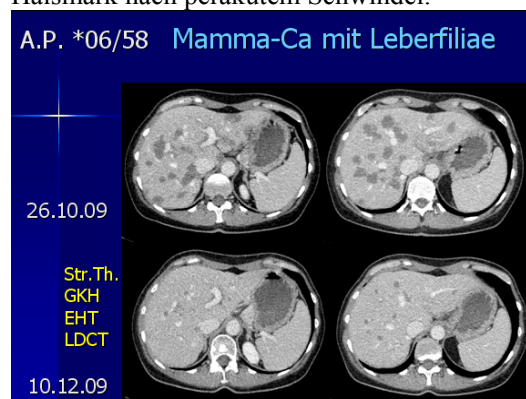


Am 20.12.'09 fiel nur noch eine kleine Verschorfung li.-thorakal auf, die wenige Tage nach der Aufnahme abfiel.

Unter der Radiatio der rechten Seite Diagnose von multiplen Lebermetastasen → Radiatio auch der gesamten Leber unter Nutzung der o.g. Chemotherapie mit Erlangung einer Vollremission intrahepatisch und Remission des Ca 15-3 unter postradiotherapeutisch begonnener DC-Immuntherapie. Zur Stabilisierung der hepatischen Remission mäßig verträgliche auswärtige Chemoembolisation. Danach aus Kostengründen keine Therapiefortsetzung, sondern Wechsel auf internistisch-onkologisch applizierte Polychemotherapie. Unter der Therapie unbeeinflussbarer rezidivierter Tumprogress in Leber und Thoraxwand, aber keine Wiederaufnahme der ursprünglichen Therapie mehr.

Fall 4 Primärhistologie: Mammakarzinom

Zwei Monate nach Ablatio mammae re. wegen eines Mammakarzinoms nach Vergrößerungsplastik (Silikonkisseneinlage) im Tumorstadium T3, N1, M0 werden bei der Pat. A.P., geb. Juni 1958, multiple (> 50) Lebermetastasen zwischen 5 und 30 mm Größe diagnostiziert. Eine adjuvante FEC-Chemotherapie hatte die Patientin abgelehnt. Diese Behandlung hätte die fast synchron zur OP klinisch apparent werdende Lebermetastasierung nicht mehr verhindern können, und mangels Liquorgängigkeit wohl auch nicht eine 14 Monate post Primäroperation diagnostizierte kleinknotige Filialisierung in Zerebrum, Zerebellum und Halsmark nach perakutem Schwindel.



Von den vier oberen CT-Schnittbildern zeigen die oberen zwei Aufnahmen während der portalen KM-Phase die Situation vor Therapiebeginn und die unteren zwei Aufnahmen sechs Wochen später schon eine eindeutige Teilremission, wobei letztere zu diesem Zeitpunkt die Herde deutlich kleiner, aber noch nicht verschwunden dokumentieren.

Von den unteren 8 Aufnahmen (portalvenöse KM-Phase) stellen die linken vier nochmals die Situation vor Behandlungsbeginn dar und die rechten vier Bilder der entsprechenden Ebenen ein Jahr später eine Vollremission.

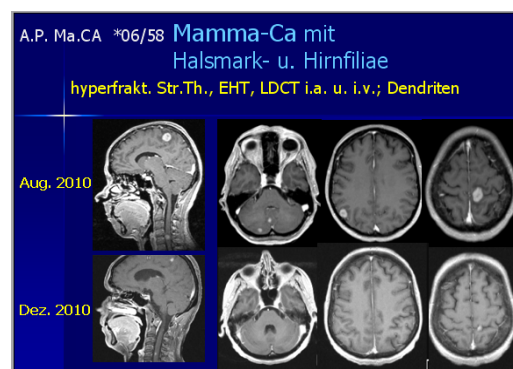
Während dieser Zeit normalisierten sich auch die Tumormarkertiter: das Ca 15-3 lag zur Zeit der Primär-OP bei 75U/ml, vor Beginn

der Lebertherapie bei 120 U/ml und nach Erhalt der ersten Vollremission vor klinischer Apparenz von Hirnmetastasen bei < 18 U/ml (s. unten)

Behandelt wurde die Patientin nach Diagnose der Lebermetastasen (Okt. 2009) über drei Wochen mit einstündiger EHT beider Leberlappen (3-4mal wöchentlich bis 150 Watt, großer Applikator) und einer simultanen Lowdose-Endoxantherapie (50 mg pro die), bis zum Start einer synchronen, hyperfraktioniert akzelerierten Chemoradiotherapie der gesamten Leber (Enddosis 22 Gy, Einzeldosis 1,2 Gy, 2mal täglich mit mind. 6 Std.-Intervall). Parallel wurden mit wenigen Tagen Intervall mehrmals Mitomycin-i.v.-Bolusinjektionen á 5 mg und Carboplatin-Kurzinfusionen á 50mg unter Ondansetrone-Übelkeitsprophylaxe verabreicht.

Nach Erreichen dieser Remission, die sich noch bis zur Vollremission auf den Aufnahmen unten, 1 Jahr nach Therapiebeginn, steigern ließ, wurde probatorisch zum Erhalt bzw. zur Verlängerung des Ergebnisses eine auswärtige **Chemoembolisation** der Leber mit Epirubicin durchgeführt, die klinisch mit anschließend 5 Mo lang stark erhöhten Transaminasen sehr schlecht vertragen wurde.

Als Versuch, die Lebervollremission zu erhalten, wurden mehrmals in zeitlich enger Kombination mit EHT-Anwendungen eigene, klinisch sehr gut tolerierte intraarterielle und portalvenöse LDCT-**Chemoperfusionen** der Leber mit Carboplatin via Leber- und Milzarterie zur Remissionserhaltung durchgeführt, worunter sich sogar langsam die Transaminasen wieder normalisierten.



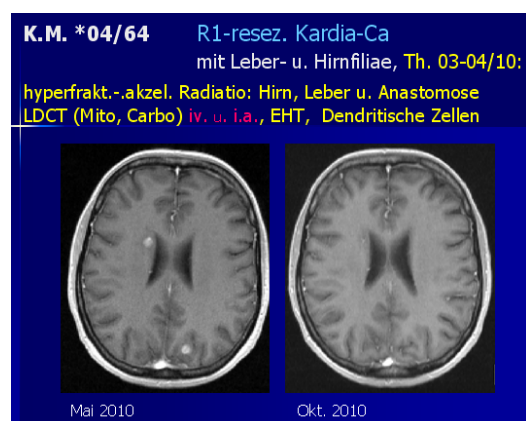
Nach Diagnose von ca. 8 Hirnmetastasen im Okt. 2010 erfolgte umgehend eine Bestrahlung von Ganzhirn und Halsmark bis 39 Gy mit 3,0 Gy ED plus EHT und LDCT sowie anschließend eine DC-Therapie mit 3

Impfungen. Darunter sind innerhalb von 2 Monaten die Kleinhirnmastasen vollständig verschwunden, die Großhirnmastasen und die Filia im Halsmark zumindest deutlich an Größe rückläufig.

Vor Start der Hirnbehandlung stieg das Ca-15-3 auf > 20 U/ml, verharrte aber Ende Dez. 2010 nach dem Eintreten der Remission auch hier wieder bei ca. 17 U/ml. Eine Remissionserhaltung in Groß- und Kleinhirn wurde ebenfalls eigenständig per selektiver intraarterieller Chemoperfusion und EHT angestrebt.

Fall 5 Primärhistologie: Kardiakarzinom

46jährige Patientin mit Z.n. R1-reseziertem Kardiakarzinom mit gleichzeitig diagnostizierten multiplen Hirn- und Leberfiliae

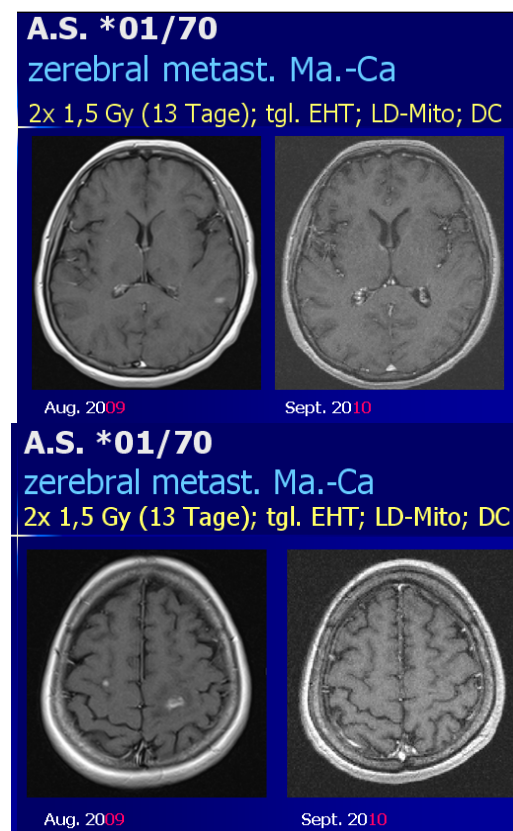


Nach gleichzeitiger Therapiekombination aus lokaler/ lokoregionärer EHT, hyperfrakt. akzel. Radiotherapie von Hirn (2x 1,5 Gy ED täglich bis 36 Gy) und Leber (2x 1,2 Gy ED/ die bis 19,2 Gy GD) sowie LDCT mit Mitomycin und Carboplatin Entwicklung einer Vollremission, die intrahepatisch 5 Monate andauerte und intrazerebral seit 8 Monaten anhält. So ist die li.-okzipitale Metastase zur Zeit genauso wenig nachweisbar wie die Metastase neben dem vorderen Drittel des rechten Seitenhornes

Nachdem aktuell im auswärtigen CT eine weitere Lebermetastase und nochmals kleine zahlenmäßig vermehrte Lymphknoten paraaortal erkennbar wurden, wird derzeit überlegt, wie man dieses intraabdominelle Rezidiv doch noch einmal beseitigen kann, zumal der ehemals stark erhöhte Tumormarkertiter des Ca 19-9 seit erster Remission nur geringfügig - innerhalb des Normalbereichs - angestiegen ist.

Fall 6 Primärhistologie: Mammakarzinom

Die 40jährige Patientin mit Hirnmetastasen sowie ossären und Lymphknotenfiliae eines Mammakarzinoms im Bereich des Mageneingangs lehnte Chemotherapieoptionen für sich ab und suchte stattdessen nach einer symptomarmen „Ausweich-“Therapie.



Die li.-seitigen MRT-Aufnahmen nach i.v. KM-Gabe im Aug. 2009 beinhalte okzipitoparietal links sowie bds. hochparietal bzw. hoch parietookzipital insgesamt drei kontrastierende metastatische Rundherde, die elf Monate später im Sept. 2010 auf den zugehörigen re.-seitigen Aufnahmen nicht mehr nachweisbar sind.

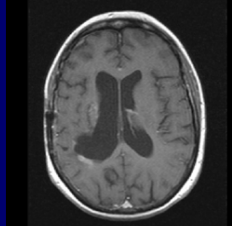
Auch im Januar 2011 ist die Patientin zerebral und hepatisch unauffällig. Zwischenzeitlich aufgetretene subkutane und re.-axilläre Metastasen konnten per weiterer Kombinationstherapie ohne Nebenwirkungen und ohne Einschränkung der Lebensqualität wieder fast vollständig zurückgedrängt werden. Seit Aug. 2010 regelmäßig durchgeführte systemische Immuntherapie mit dendritischen Zellen.

Fall 7 Primärhistologie: Glioblastoma multiforme Grad IV WHO

Im Oktober 2006 (38-jährige Patientin) Primärdiagnose eines Glioblastoma multiforme mit nachfolgender Resektion und anschließender Standard-Chemoradiotherapie mit Temodal. Im April 2007 1. Rezidivtumor-OP und nachfolgend schlechte Verträglichkeit des Temodal. Im Juli 2007 Beginn einer kombinierten DC-Therapie und regelmäßiger EHT-Anwendungen bis Dez. 2010. Darunter 3 kleine Tumorrezidive mit minimaler Symptomatik, aber sofortiger MRT-Diagnostik und umgehender Resektion. Mehrfache Abwandlung des Dendritenpriming, auch unter Nutzung autologen Tumormaterials; Erhoffte Wirkungsverstärkung der Dendriten u.a. durch Impfungen mit onkolytischen Viren. Aufgrund einer Post-OP-Komplikation nach der 4. Lokalrezidivresektion li.-seitige Halbseitenparese.

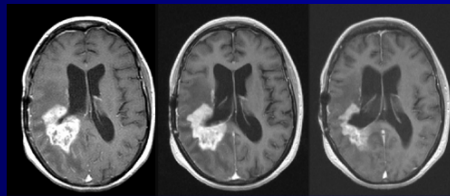
K.K. *01/68 5x rezidiv. Glioblastom seit 2006
EHT + Dendr. Z. seit Juni 2007 (nach 1. Rez.-OP)

11.03.10 5 Mo. nach dem 4. Lokalrezidiv



K.K. *01/61 5x rezidiv. Glioblastom seit 10/06
EHT + DC seit Juni 2007 nach 1. Rez.-OP 04/07

seit 05/10: EHT; LDCT + NDV i.v. und i.a.; DC
05.05.2010 29.06.2010 03.09.2010



Die vier MRT-Aufnahmen der gleichen Schnittebene nach i.v. KM-Gabe zeigen einerseits, dass (diesmal ohne Begleitsymptomatik) innerhalb von nur 7 Wochen zwischen 11.03. und 05.05.2010 ein fast vier cm großes Tumorrezidiv im ursprünglichen Tumorbett entstehen kann, und dass dieses anschließend unter DC-Therapiefortsetzung, regelmäßigen EHT-Applikationen (3x wöchentlich) und gleichzeitigen intravenösen sowie superselektiven intraarteriellen Mitomycingaben (3,0

bis 6,5 mg) in die Aa. cerebri media und posterior der Rezidivtumor über vier Monate bei uneingeschränkter Lebensqualität unter Berücksichtigung der Halbseitenparese wieder etwas geschrumpft ist.

Erst ein weiterer Tumorprogress im November 2010, 4½ Jahre nach der Primärdiagnose war nicht mehr zu stoppen und führte Ende 2010 ad exitum.

Fall 8 Primärhistologie: Glioblastoma multiforme Grad IV WHO

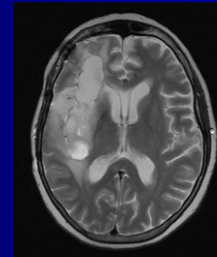
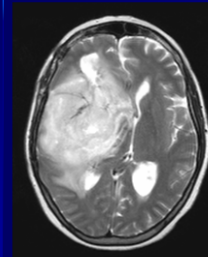
Im Juli 2006 bei hochschwangerer 34-jähriger Patientin Diagnose eines inoperablen Primärtumors; → Entbindung per Kaiserschnitt in der 32. Schwangerschaftswoche und stationäre Entlassung, da unter Berücksichtigung des riesigen Tumors und des Wochenbettes klinischerseits kein Sinn in einer Standardchemoradiotherapie mehr gesehen wurde. Daraufhin umgehender Start einer DC-Therapie, kombiniert mit EHT, 3mal wöchentlich.

L.M. 34 J. Glioblastoma multiforme

EHT, NDV, DC verst. März '07

Juli 2006

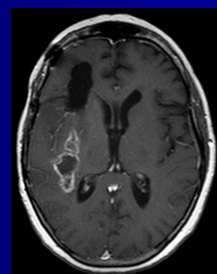
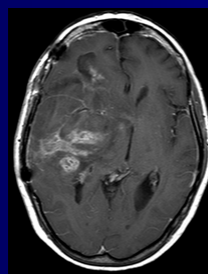
Nov. 2006



L.M. 34 J. Glioblastoma multiforme

Juli 2006

Nov. 2006



Gezeigt wird jeweils die gleiche Schichtebene, dabei auf den beiden li.-seitigen MRT-Aufnahmen der Zustand vor Therapie und auf den beiden re.-seitigen der Zustand nach vier Monaten erfolgreicher Therapie:

die beiden oberen Aufnahmen, T2-gewichtet mit wasserhaltig signalintensiven hellen Ödemzonen weisen im Verlauf auf die

deutliche therapeutisch bedingte Verringerung des perifokalen Ödems hin, die beiden unteren kennzeichnen T1-gewichtet die Verringerung der Tumorgroße selbst, wobei der Resttumor nur noch durch einen länglichen schmalen Kontrastmittelsaum markiert ist, der zentral eine flüssigkeitsäquivalente zystoide Signalfreiheit aufweist.

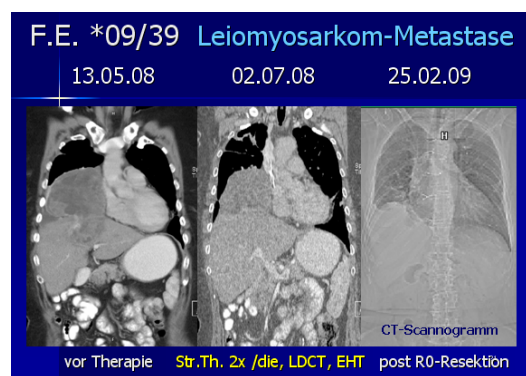
Auffällig ist auf beiden re.-seitigen Aufnahmen zur Darstellung der Behandlungsergebnisse das Verschwinden der Mittellinienausbiegung nach links und die konsekutive Wiederentfaltung der re.-seitigen Ventrikelanteile als weiteres Remissionszeichen.

Klinisch beendet war die Remission nach 7 Monaten im Feb. 2008. Die Patientin verstarb im März 2008 infolge des Tumorprogresss.

Fall 9 Primärhistologie: niedrig differenziertes Stromasarkom des rechten Ovars

68-jährige Patientin mit einer solitären inoperablen Metastase eines ehemaligen Stromasarkoms des re. Ovars, welche vom re. Leberlappen aus das Zwerchfell perforiert hatte, den rechten Unterlappen hochgradig infiltrierte und mind. 1/3 des re. Thoraxlumens einnahm.

Bei schlechten Blutgasparametern und hochgradiger Ruhedyspnoe wurden chemotherapeutische Optionen von Seiten der behandelnden internistischen Onkologen abgelehnt.

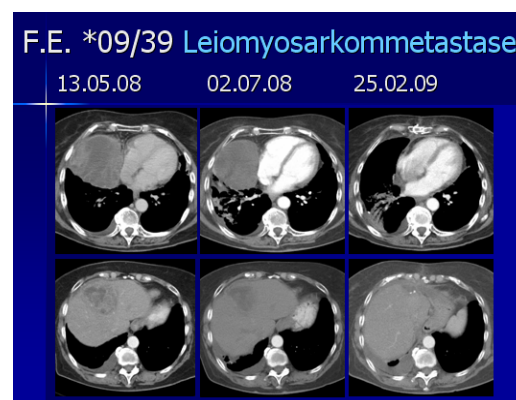


Nach Beginn einer neoadjuvanten Kombinationstherapie mit täglicher EHT unter simultaner Chemoradiotherapie, hyperfraktioniert akzeleriert bis 48 Gy GD, 2mal 1,5 Gy täglich und synchron mehreren LDCT-Mitomycin-Gaben Erreichen einer Teilremission bis in die R0-Resektabilität hinein.

So zeigt die erste der beiden zweidimensionalen koronaren CT-Rekonstruktionen, dass die Metastase

intrahepatisch (mittleres Bild) weniger auffällig zur Darstellung kommt als auf dem linken prätherapeutisch angefertigten, und dass posttherapeutisch wieder ein re.-lateralen phrenikokostalen Randwinkel bis zum Zwerchfell hinab einsehbar wurde. Die rechte Aufnahme, ein ventrodorsales CT-Scannogramm als Summationsaufnahme zeigt eine wiedergewonnene vollständige Transparenz der rechten Lunge nach erfolgreicher Entfernung des Lungenunterlappens.

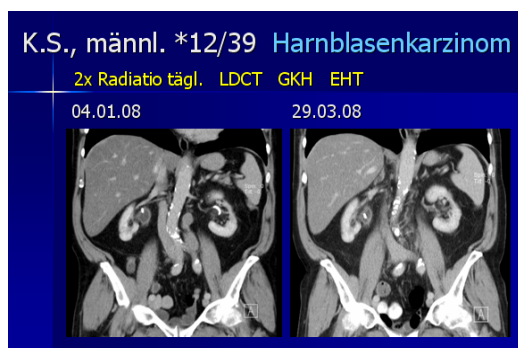
Zu den nachfolgenden sechs computertomographischen Aufnahmen nach KM-Gabe i.v.: Die transversalen Schnittbilder dokumentieren in der arteriellen Phase auf den mittleren Bildern (oben intrapulmonal, unten intrahepatisch) die Verkleinerung der Metastase im Gegensatz zur prätherapeutischen Situation der li.-seitigen Aufnahmen, während die re.-seitigen Bilder postoperativ keinen Tumor mehr abbilden, sondern nur noch einen geringen Pleuraerguss.



8 Monate post OP später wurde im April 2009 per CT ein kleines Lokalrezidiv diagnostiziert, das auswärtig frustran polychemotherapeutisch behandelt wurde, bis die Patientin im Juni 2009 in klinisch ähnlich schlechtem Zustand wie ein Jahr zuvor in unregelmäßigen Behandlungsintervallen wieder eine EHT-Behandlung und LDCT mit mehrmals Mitomycin (3,5 mg) aufnahm. Deren positive klinische Wirkung mit deutlichem Rückgang der Dyspnoe endete im Oktober 2009. Ende November 2009 verstarb die Patientin in der respiratorischen Insuffizienz.

Fall 10 Primärhistologie: Urothelkarzinom der Harnblase (pT3, N2, Mx; G3)

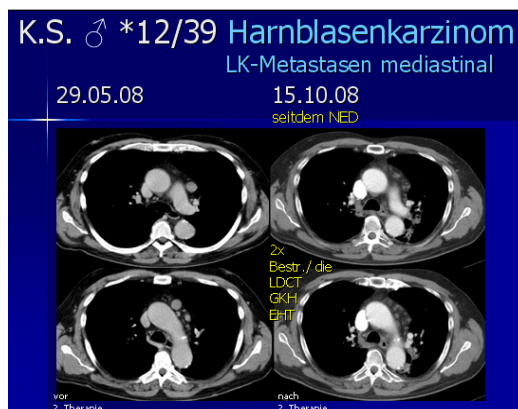
2005 Z.n. Neblasenentfernung wegen postoperativer Rektumnahtinsuffizienz mit Peritonitis und konsekutiver perkutaner Nierenfistelung bds. Im Dez. 2008 Diagnose eines retroperitonealen Lymphknotenmetastasenrezidivs unterhalb der linken Nierenvene in loco typico.



Zwischen Jan. und März 2008 Anwendung einer hyperfraktioniert akzelerierten Chemoradiotherapie mit LDCT (mehrmals jeweils 5 mg Mitomycin als i.v. Bolusinjektion sowie 50 mg Carboplatin-Kurzinfusionen) und parallel 4mal wöchentlichen EHT-Applikationen sowie einzelnen GKH-Anwendungen.

Auf dem linken, zweidimensional koronar rekonstruierten CT-Bild erkennt man links von von der Aortenbifurkation zwei untereinander gelegene, metastatisch vergrößerte Lymphknoten, die 4 Wochen nach Chemoradiotherapie bei der Befundkontrolle in gleicher Schichtebene verschwunden sind.

Am gleichen Untersuchungstag fanden sich jedoch auch Lymphknotenmetastasen im bis dato unbehandelten Mediastinum (s. nachfolgende CT-Aufnahmen):



Die beiden li.-seitigen Aufnahmen zeigen auf der oberen lateral der li. A. pulmonalis eine kleine kugelige Metastase und auf der unteren

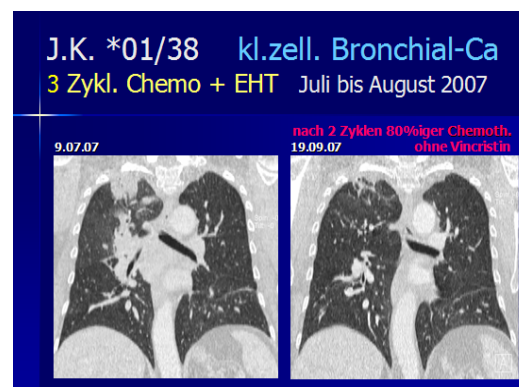
weitere kleine Metastasen li.-lat. des Aortenbogens.

Die beiden rechtsseitigen Bilder dokumentieren nur noch harmlose kleinste Lymphknoten im umgebenden hypodensen mediastinalen Fettgewebe.

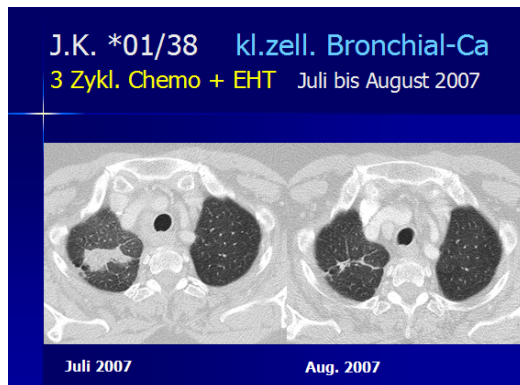
Fall 11 Primärhistologie: Kleinzell. Bronchialkarzinom

Bei einer 69-jährigen Patientin fällt infolge Anstrengungsdyspnoe angefertigter p.a.-Thoraxübersichtsaufnahme eine Verbreiterung der oberen Mediastinalhälfte auf. Bronchokopisch wird der CT-Verdacht auf ein Bronchialkarzinom mit ausgedehnten Lungenmetastasen pathohistologisch als kleinzelliges BC bestätigt. Die daraufhin begonnene Polychemotherapie wird über drei Monate hinweg von regelmäßigen EHT-Behandlungen (bis 3mal wöchentlich) begleitet.

Die nachfolgenden, sich entsprechenden zweidimensional rekonstruierten CT-Schichten belegen im Lungenmodus das Verschwinden des Primarius in der rechten Pleurakuppel nach dem dritten Chemotherapiezyklus, der wegen Nebenwirkungen wie der zweite Zyklus zuvor ohne Vincristin und unter Dosisminderung der übrigen Medikamente durchgeführt werden musste:

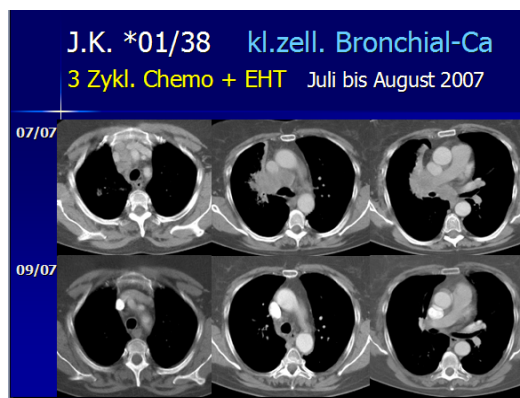
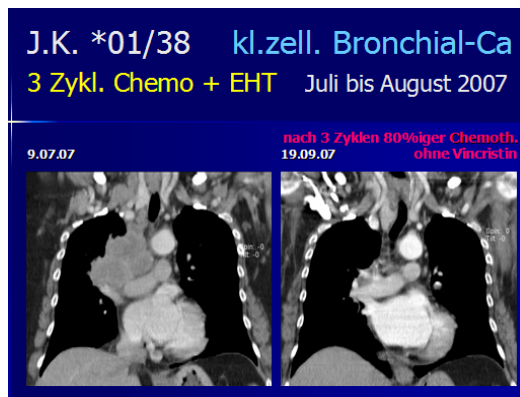


Es folgten noch eine Ergebnis-stabilisierende Kombination aus Strahlentherapie bis 50 Gy und EHT samt nomofraktionierter prophylaktischer Strahlentherapie des Hirns bis 30 Gy GD (2,0 Gy ED) und anschließend mehrere DC-Impfungen, die die klinisch symptomatische Ausbildung einer multilokulären, Schicksal-entscheidenden Hirnmetastasierung ein halbes Jahr später nicht verhindern konnten. Eine weitere Kausaltherapie fand zugunsten rein pflegerischer Maßnahmen nicht mehr statt



Auch auf der transversalen Schichtung erkennt man im Lungenmodus prätherapeutisch die solide Raumforderung in der re. Pleurakuppel, während nach Behandlungsende nur noch dünne, narbige Streifen hiervon verblieben sind.

Auf den nachfolgenden Aufnahmen weist die zweidimensionale koronare CT-Rekonstruktion prätherapeutisch im linken Bild auf große Lymphknotenpakete innerhalb der oberen Mediastinalhälfte auf, die sich bis in die untere Halshälfte kranialwärts fortsetzen, während posttherapeutisch in der rechten, korrespondierenden Schichtaufnahme solche Weichteilvermehrungen nicht mehr nachzuweisen sind:



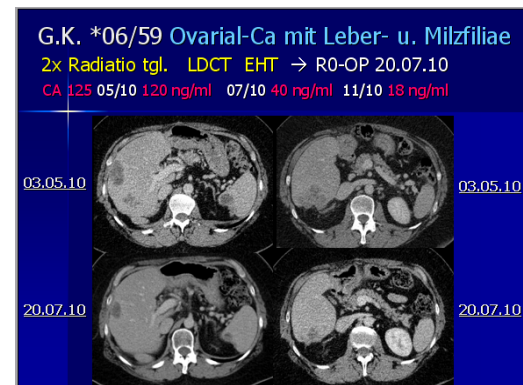
Ein analoger Befund ist auf den transversalen Aufnahmen erkennbar:

Auf den drei oberen Bildern erkennt man linksseitig ein Weichteilplus im linken oberen Mediastinum hinter dem Jugulum, das sich im mittleren kaudal unterhalb des Aortenbogen wieder findet und im rechten Schnittbild bis zum Lungenhilus hinunterreicht. Posttherapeutisch ist in exakt den gleichen Schnittebenen nichts mehr von den pathologischen Raumforderungen dokumentiert.

Fall 12 Primärhistologie: Ovarialkarzinom

Nach multiplen Chemotherapieversuchen über ca. 5 Jahre hinweg, zuletzt frustan, unterzog sich die 50-jährige Patientin mit progredienten multiplen Leber- und Milzmetastasen einer simultan kombinierten EHT, LDCT mit Mitomycin (bei Carboplatinallergie!) und hyperfraktioniert-akzelerierten Strahlentherapie der ganzen Leber sowie der Milz.

Die nachfolgenden Aufnahmen verdeutlichen auf korrespondierenden CT-Schichten in der portalen Kontrastmittelpase, dass die zwei größten Lebermetastasen und die intrasplenale Metastase am Milzhilus - hier gemeinsam abgebildet - infolge der Kombinationstherapie zwischen Mai und Juli 2010 deutlich verkleinert dokumentiert sind. Der Serum-Tumormarkertiter für das Ca-125 wies einen entsprechend sinkenden Verlauf auf: 120 ng /ml im Mai, 40 ng /ml im Juli und postoperativ nach 2-facher hepatischer Metastasektomie und Splenektomie (August) nur noch 18 ng /ml im November 2010.

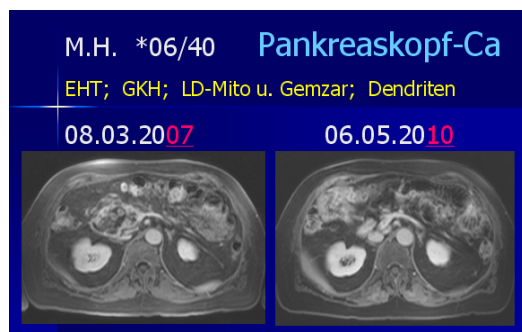


Im Januar 2011 zeigte sich eine diskret ansteigende Titertendenz des Ca-125 auf 24 ng /ml, und das PET-CT detektierte daraufhin drei kleine Rezidivherde im Coecumpolbereich, die sich aktuell pathohistologisch als kleine Tumorzidive bestätigen ließen, so dass eine DC-Therapie wiederaufgenommen werden soll, zusammen mit der Kombination aus einer

intermittierenden superselektiven Chemoperfusion (A. mesenterica) und EHT.

Fall 13 Primärhistologie: Pankreaskopfkarzinom

Bei Erstdiagnose 66-jähriger Patient mit chronisch rezidivierender Pankreatitis, mäßiger CEA- und Ca-19-9-Erhöhung; konsekutiv mehrfach (negative) perkutane Feinnadelstanzbiopsien im Okt./ Nov. 2006 aus sonographisch echoarmem Pankreaskopf. Im Feb. 2007 pos. Feinnadelbiopsie bei endoskopischer Pankreaskopf-Sonographie; daraufhin umgehende Whipple-OP und vorherige EHT mit 2-maliger Mitomycin-LDCT über eine Woche. Post OP Versuch einer adjuvanten Standard-Gemzartherapie in Kombination mit EHT; Abbruch wegen Grad IV-NW mit akuter rechts-/ Linksherzinsuffizienz, Ruhedyspnoe und massiven Beinödemen: Gemzartherapie-Abbruch und nach klinischer Besserung hyperfrakt. akzelerierte Radiotherapie plus simultane LDCT (mehrfach 5 mg Mitomycin), EHT und DC-Therapie über vier 4 Jahre mit ständiger Verlängerung der Impfintervalle. Zur Zeit anhaltende Tumorfreiheit mit hervorragendem AZ.



Das linke MR-Tomogramm zeigt am 08.03.2007 einen auf knapp 8 cm vergrößerten Pankreaskopf, der zentral in einer T2-gewichteten Sequenz einen signalintensiven, zystoiden Tumorbefund von ca. 5 cm Größe aufweist, der sich nach i.v.-Enhancing auf dem rechten Bild inhomogen kontrastiert. In der unteren/ mittleren Aufnahme der dreidimensionalen MRCP-Rekonstruktion erkennt man den vergrößerten Pankreaskopf und den bei chronischer Pankreatitis typisch schraubenförmig gewundenen Pankreasgang.

Während auf der ersten Aufnahme li.-seitig nochmals prätherapeutisch der große inhomogene karzinomatöse Pankreaskopftumor abgebildet ist, weist - jeweils nach i.v.-KM-Gabe

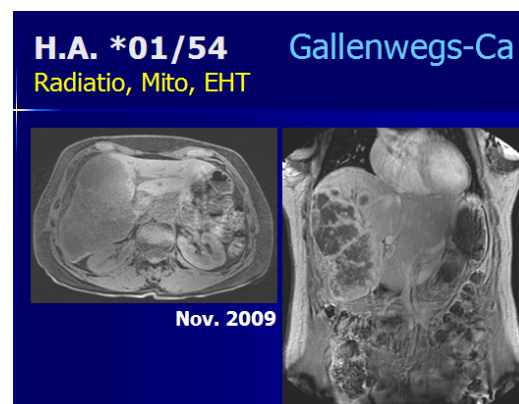
auf absolut korrespondierenden Schnitten - zeigt die gleiche Schnittebene im Mai 2010 absolut unauffällige Verhältnisse, bzw. nur einen kleinen Jejunalschlingenanteil in der ehemaligen Pankreaskopfloge.

Pathohistologisch maß das mittelgradig differenzierte Adenokarzinom das Pankreaskopfes noch 5 cm im größten Durchmesser. Lymphknotenmetastasen fanden sich intraoperativ nicht.

Zur Zeit anhaltend klinisch sehr guter Allgemeinzustand ohne Tumorrezidivverdacht bei unauffälligen Tumormarkertitern.

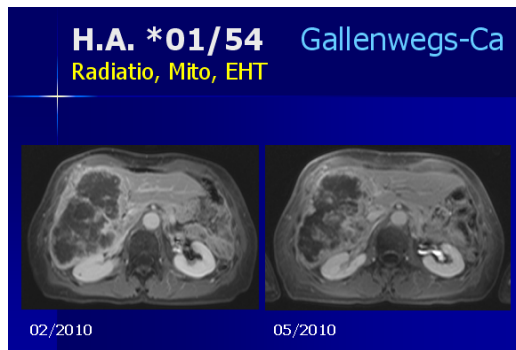
Fall 14 Primärhistologie: Gallenwegskarzinom

Inoperables Gallenwegskarzinom bei 55-jähriger Patientin, die im Nov./ Dez. 2009 eine kombinierte hyperfrakt. akzelerierte Strahlentherapie in simultaner Kombination mit mehrmals 5 mg Mitomycin und regelmäßig EHT erhielt. Eine damals bekannte, nur sehr langsam progrediente beidseitige Lungenmetastasierung wurde bislang (Jan 2011) nicht therapiert. Im Sommer 2010 bei Zunahme des Ca 19-9 nochmalige LDCT und EHT, ohne Radiotherapie. Darunter wieder Tumormarkerabfall bis Dez. 2010. Wegen Wiederanstiegs bei sehr gutem klinischen Befinden evtl. kurzfristig nochmalige LDCT-/ EHT-Kombination.



Beide MRT-Aufnahmen zeigen prätherapeutisch den fast vollständig karzinomatös umgewandelten re. Leberlappen, wobei die rechte Aufnahme in der koronaren Aufsicht nach i.v. KM-Gabe die konsekutive Hyperplasie des linken Leberlappens veranschaulicht, der den Magen nach links-lateraldrängt und rechtsseitig von den inhomogenen Tumorstrukturen des rechten Lappens abzugrenzen ist, die eine ähnliche

Signalstruktur aufweisen wie das kaudal angrenzende Querkolon.



Das linke CT-Bild aus Feb. 2010 zeigt eine minimal geringere Tumorausdehnung als das MR-Tomogramm von November 2009, und die rechte CT-Aufnahme auch im Mai 2010 noch keinen eindeutigen Progress.

Fall 15 Primärhistologie: Lymphoepitheliales Sarkom

Bei dem 67-jährigen Patienten kam es im Feb. 2008 zu einer kleinen nicht abheilenden ulzerösen Verschorfung an der Kopfhaut der Stirn im Bereich des Haaransatzes, die schnell größere wurde. Im März 2008 wurde bei gleichzeitig tastbar vergrößerten Lymphknoten der linken Halsseite bioptisch/ pathohistologisch die Diagnose eines seltenen lymphangioepithelialen Sarkoms der Kopfschwarte gestellt, ohne dass man in der Universitätsklinik Hamburg zu diesem Zeitpunkt noch therapeutische Optionen sah.



Die beiden oberen Abbildungen zeigen prätherapeutisch die schnelle Progredienz des Tumors innerhalb von 2 Monaten, während die untere Aufnahme die posttherapeutische Situation 2 weitere Monate später wiedergibt.

Behandelt wurden die Tumorregion und die Lymphknoten der linken Halsgefäßscheide hy-

perfrakt. akzeleriert bis 50,4 Gy ED bei 2 x 1,2 Gy ED täglich, in simultaner Kombination mit einer Chemotherapie aus Navelbine, 1x 2 mg i.v. und 2x 50 mg Cardioxane, jeweils pro Woche sowie einer parallelen EHT, 4x wöchentlich, ergänzt durch synchrone GKH- und hierin integrierte OFH-Applikationen, möglichst an Tagen der bestens vertragenen Chemotherapie.

Die bei dem Patienten zusätzlich durchgeführte DC-Therapie dürfte dazu geführt haben, dass bei ihm bis heute keine systemische Metastasierung aufgetreten ist, insbesondere keine Lungenmetastasierung.

Zusammenfassung der Kombinationsbausteine im Einzelnen:

Strahlentherapie

- GD bis ca. 50 Gy
 - ED 1,8 Gy nomofraktioniert
- GD ca. 20 bis ca. 45 Gy
 - ED 1,1 bis 1,5 Gy hyperfraktioniert akzeleriert 2x pro die mit (6-)7 Std. Intervall
- ED 2,5 bis 4 Gy hypofraktioniert, nicht unbedingt täglich, sondern mit 2-4 Tagen oder einer Woche Abstand hochpalliativ

Lowdose Chemotherapie

- Mitomycin 3-5 mg / qm KOF
- Carboplatin 30-50 mg / qm KOF
- Gemzar 300-500 mg / qm KOF
- Endoxan oder 50 mg tgl. (1 Tbl. abends)
- Ixoten 50 mg tgl. (1 Tbl. abends)
- 5-FU 200-300 mg / qm KOF
+/- Ca-Folnat 100-200 mg / qm KOF
- Vindesine + 2 mg Absolutdosis
- Cardioxane 50 mg Absolutdosis

Ganzkörperhyperthermie (GKH)

- Dauer bis zu 3 Std., davon mind. 1 Std. mit Kern-Temp. > 38 Grad Celsius
- anschließend 1 Std. EHT

Oberflächenhyperthermie (OFH) immer in Kombination:

- Dauer 1 Std.
 - evtl. als Teil einer Ganzkörperhyperthermie (GKH), falls Infrarot-GKH,
 - anschließend EHT

Gesamtorgan-Str.-Therapie

- **Hirn** 2 x 1,5 Gy / die → 39,0 Gy
- Rückenmark dito bis 45 Gy (Feldlänge!!)
- **Leber** 2 x 1,2 Gy / die → 19,2 Gy
- **Lunge** 2 x 1,1 Gy / die → 19,8 Gy
ggf. bd. Lungenhälften sequentiell
- *Lymphknotenregionen und Skelettsystem
nicht bei diffusem Befall*

Cave:

- Mitomycin-Applikation strengstens i.v. und nie kombiniert mit einer Lungenbestrahlung wegen Pneumonitis- mit Lungenfibrose-Risiko!!
- Antibiotika-ähnliche Allergien möglich
hämolytisch-urämisches Syndrom möglich
- Gemzarwirkung deutlich verspätet durch Verstoffwechselung zum wirksamen Medikament
- Gemzar-Pneumonitiden ebenfalls möglich
- Carboplatin-bedingter Nadir für Thrombos u. Leukos mit ca. 3-wöchigem Intervall

Cave:

- Akkumulierung der Knochenmarkstoxizität bei Lowdose-Polychemotherapie (LD-PCT)
- **Endoxanblase!!** Zystitisrisiko mit Schrumpfung bei Dauertherapie
- Anamnestisch keine systemischen Lungenvorerkrankungen
- anamnestisch keine Hepatitis B oder C

**The Immune Regulating Effect of Hyperthermia in
Combination with TCM on Cancer Patients**

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The Immune Regulating Effect of Hyperthermia in Combination with TCM on Cancer Patients

ABSTRACT

In recent years, as the development of integrative cancer treatments, hyperthermia and Traditional Chinese Medicine (TCM) have become significant methods of treating cancer, and the immune regulating effects of them have attracted more and more attentions. In this text, depending on the clinical research data of Clifford Hospital from 2009 to 2013, research progress of hyperthermia in the world, and research achievements of TCM, we discussed the immune regulating effect of hyperthermia in combination with TCM on cancer patients, and its potentiality in anticancer treatments.

1. Introduction

As heating and temperature detecting techniques have continuously improved, hyperthermia has become another significant method of treating cancer after surgery, radiotherapy, and chemotherapy. Research showed that killing cancer cells did not only depend on extrinsic sources of treatment, but also depend on the immunity of the body itself. With the rise of importance of hyperthermia in cancer treatments, the immune regulating effect of hyperthermia has gained more and more attentions. TCM is an important method for treating cancer in China. Immune regulating effect is the biggest advantage and feature of TCM in treating cancer. The main advantages of immune regulating of TCM are: improving the internal environment of human body, especially the microenvironment; helping patients to survive with tumor; and preventing the metastasis and recurrence. These features are consistent with the trends of cancer treatment in recent years, which are changing the focus from purely killing cancer cells to interfering the microenvironment of their occurrence and progress, with the treatment strategy of targeting the cancerous microenvironment. Hyperthermia and TCM are both important methods of integrative cancer treatments. So far there are many experimental and clinical research on the immune effect of hyperthermia and TCM on cancer patients. In the past clinical practice at Clifford Hospital, we have focused on the non-toxic integrative cancer treatments, and the combination of hyperthermia and TCM has obtained definite curative effects. We will discuss the role of the immune regulating effect of hyperthermia in combination with TCM on cancer patients based on the review of our clinical data and the study progress of other reported research.

2. Immunological effect of hyperthermia

2.1 Induction of anticancer immunity of local hyperthermia

In the process of local hyperthermia, after treatments on primary focus, doctors found that not only the primary focus disappeared or reduced, but also metastases did; or after treatments on metastases, primary focus also appeared or reduced. This is called the abscopal effect of cancer hyperthermia. We recognized that the immunological effect induced by hyperthermia had significant influence on the reduction of the size of primary tumor and metastatic of site. The anticancer immunity which were induced by local hyperthermia included the reinforcement of immunological effect of NK cells, T-lymphocytes and macrophages.

Hu Yongcheng, et al. found that the activity of NK cells increased in mice with transplanted tumor after hyperthermia, and the speed of growth and size of the primary tumor decreased, and the occurrence of lung metastasis decreased^[1].

Kubista, et al. applied hyperthermia to treat osteosarcoma and chondrosarcoma. They found that, after applying hyperthermia, anticancer activity induced by NK cell increased, and the nonspecific immunity NK cell played an important role in controlling the growth of cancer, killing cancer cells in the circulation, and preventing and reducing hematogenous dissemination^[2].

2.2 Cancer hyperthermia and immunostimulation

In 1969, Strauss indicated that the decomposed product of cancer cell degeneration and necrosis was absorbed by the body after hyperthermia, which stimulated the immune system to generate anticancer immunity as a kind of antigen. Researchers in China applied hyperthermia on mice with transplanted tumors in their lower limbs, and found that: in the 43°C and 45°C groups, lung metastases were reduced, and the activity of NK cells was raised; in the 47°C group, because the temperature was too high, some lower limbs fell off, lung metastases were more than those in 43°C and 45°C groups, and NK cell activity was not raised at all. This phenomenon proved the importance of necrosis and decomposition products in increasing the immunity of the body.

Wu Yu, et al. applied radiofrequency ablation in treating lung cancer. They detected lymphocytes, and found that after treatments, the cellular immune function of patients was stimulated. Luo Baoming, et al. concluded in their research that radiofrequency ablation could improve the immunosuppression state of liver cancer patients at certain levels^[3, 4].

2.3 Immunological reaction induced by non-specific inflammatory reaction

Local hyperthermia is a kind of physical injury factor, which can cause non-specific inflammatory reactions. Inflammatory reactions can induce immunological reactions by dissolvable cell factors such as IL-1.

Morita, et al. observed that hyperthermia could increase lymphocyte infiltration (LI) in parts of the tumor of patients with esophagus cancer. The five year survival rates of patients with LI (++), LI (+) and LI (-) were 75.5%, 46.1% and 27.8%^[5].

2.4 Heat shock protein (HSP) and tumor immunity

Due to the effectiveness of some physical and chemical factors (such as viral infection, anoxia, heavy metal ions, ultraviolet ray exposure, etc.), organism cells can activate HSP gene, and selectively compose a group of highly conservative protein, which is HSP. In recent years, we found that HSP participated in specific anticancer immunological reaction of the human body, and that the expression quantity of HSP was closely related to the immunogenicity of tumor. The effectiveness of HSP in immune response has drawn wide attention of researchers^[6, 7].

Menoret, et al. recognized that after being heated, cancer cells could generate HSP, which could stimulate immune system of the body, improve immunity, and cause specific immunological reactions to the tumor^[8].

Schueller, et al. found that the expression of HSP70 and HSP90 of liver cancer cells could be reinforced after hyperthermia, which could improve immunity against hepatic cellular cancer^[9].

3. TCM and immunity

3.1 Effectiveness of TCM in tumor microenvironment

In the opinion of TCM, the occurrence of cancer is due to the functional disorder of Zang-Fu organs. Under multiple inductions of internal and external factors, the generation of etiological factors causes the disorder of Qi and blood, and Yin and Yang, in combination with the accumulation of pathological factors such as sputum, blood stasis, wetness, and hotness, breakage of the internal balance of the human body, which causes infernal circle process, and generates an internal environment that promotes the occurrence and progress of cancer. This is consistent with the recognition of tumor microenvironment. Zhou Zhongying, a famous physician of TCM and a master of traditional medicine, considers that in the multiple effectiveness of internal and external factors, a kind of pathogenic factor is generated based on the disorder of organ disorder, which is a specific causative agent of the occurrence and progress of cancer^[10].

3.2 Vital Qi in TCM and immunity

Vital Qi in TCM was called “Zhen Qi” (genuine Qi) in ancient times. It originated from the simple materialism and spontaneous dialectics thought in ancient time of China. Vital Qi is the material foundation of the human body that fights against pathogenic factors. It includes the functions and activities of YING (nutritive Qi or blood circulating in meridian), WEI(protective Qi), meridian

Qi, blood, JING (essence), spirit, JIN (lighter and clearer fluids), YE (fluids with heavier and thicker nature), Zang-fu Organs, and meridians. Vital Qi exists in either inside or outside the vessels, and runs all over the body. It has the functions of protecting the human body from pathogen, self recovery, and balance regulating^[11].

An Hui College of Chinese Medicine applied Jianpi Yiqi Decoction to 42 patients. After treatments, the T cell ratio, lymphocyte transformation rate, and number of immunoglobulin were raised. Bao Suzhen, et al used Shiquan Dabu Decoction to treat mice with liver cancer. They observed that both the T cell transformation rate and the number of neutrophilic leukocyte, the activator of NK cell, were significantly increased^[12].

Zheng Wangqiao, et al. found that after treatments of Shenqi Fuzheng Injection, the thymus index and spleen index of mice with liver cancer after chemotherapy were both higher than the control group ($P < 0.05$); the IL-2 level in blood serum of mice in the treatment group was significantly higher than the control group, and TNF- α in the treatment group was lower than that in the control group ($P < 0.05$)^[13]. Chinese formulated products Kang Lai Te Injection and Huang Qi Injection are both representatives of the methods of “supplementing Qi and nourishing Yin” and “benefiting vital energy and strengthening body resistance”.

3.3 Types and examples of immune effectiveness of TCM

According to modern pharmacology research of Chinese medicine in the recent 50 years, many kinds of Chinese medicine have different levels of immune effectiveness in the human body, which can be divided into 4 types^[14]:

3.3.1 Herbs with effectiveness on abnormal immunological reaction (allergy)

folium Perillae, radix saposhnikoviae, radix bupleuri, herba schizonepetae, herba ephedrae, rhizoma atractylodis, dryopteris crassirhizoma Nakai, fructus xanthii, fructus kochiae, cortex dictamni, radix et rhizoma rhei, cortex phellodendri, and feculae bombycis.

3.3.2 Herbs with promotion of immunity

radix astragali, ganoderma, radix ginseng, rhizoma atractylodis macrocephalae, semen coicis, caulis spatholobi, radix rehmanniae recens, [radices paeoniae alba](#), equus asinus Linnaeus, cornu cervi pantotrichum, herba cistanchis, herba epimedii, semen cuscudae, radix morindae officinalis, radix glehniae, radix ophiopogonis, fructus schisandrae chinensis, cordyceps sinensis Sacc., tremella fuciformis Berk., lycium chinense Mill., radix polygoni multiflori, polyporus umbellatus (Pers.) fries, garlic, spreading hedyotis herb, herba houttuyniae, radix salviae miltiorrhizae, rhizoma Chuanxiong, flos carthami, radix scutellariae, and rhizoma coptidis.

3.3.3 Herbs with immunodepressive effect

radix puerariae, forsythia suspensa Vahl, flos lonicerae, herba agastachis, herba eupatorii, folium isatidis, radix isatidis, herba houttuyniae, flos chrysanthemi indici, herba taraxaci, herba artemisiae scopariae, herba andrographitis, radix gentianae, fructus gardeniae, herba leonuri, cortex moutan, tripterygium wilfordii, and camptothecin.

3.3.4 Herbs with immune regulating effect

many herbs have biphasic modulation effect on immunity, such as radix astragali, radix saposhnikoviae, rhizoma atractylodis macrocephalae, radix glycyrrhizae, radix bupleuri, rhizoma atractylodis, radix pseudostellariae, radix acanthopanacis senticosi, herba artemisiae annuae, herba andrographitis, spreading hedyotis herb, Tripterygium wilfordii, and tripterygium hypoglaucom hutch.

4. Acupuncture and immunity

With the development of modern acupuncture, the research of the effect and mechanism of acupuncture on immunity have attracted more and more attention. A lot of research materials have

shown that acupuncture can change the specific and non-specific immunity of the body, significantly affect immunocyte and immunological molecule, and play a positive role in preventing and treating allergic disorders, infections, inflammatory diseases, and cancer. This effect has the characteristics of entirety and bidirectionality^[15].

Chen Liangliang, et al. applied acupuncture in combination with chemotherapy in treating 50 cases with middle and advanced staged lung cancer. Acupoints: Dayuan, Zusanli, Neiguan; with herbal point application on the acupoints of Dazhui and Feishu. The results showed that while relieving the symptoms of patients with lung cancer, the treatments could raise the low lymphocyte conversion ratio, and recover the activity of NK cells without obvious side effects. This kind of immune regulating effect of acupuncture has parallel relation with the improvement of clinical therapeutic effect^[16].

Zhao Changlin, et al did research of acupuncture on the acupoints of Zusanli, Sanyinjiao, Neiguan, Shang Juxu, Hegu, Taixi, Taichong, Yinlingquan, and Yanglingquan, with moxibustion on the acupoints of Shenque, Guanyuan, Qihai, and Zusanli. The results showed that after treatments, the number of T-lymphocyte subsets (CD3, CD4, and CD8) in the peripheral blood of patients with colon cancer and liver metastases was significantly increased^[17].

Sun Hua reported that acupuncture had a depressant effect on the accentuation of humoral immunity in patients with rheumatoid arthritis. It could lower the level of IgG, IgA, and IgM, or make them return to normal; it could also raise complement C3 and decrease the level of immune complex^[18].

5. Clinical research data of Clifford Hospital

5.1 Effect of immunity of local hyperthermia in combination with TCM treating patients with middle and advanced staged colorectal cancer

Patient resource: inpatients of Clifford Hospital from April, 2011 to April, 2012 diagnosed with middle and advanced staged colorectal cancer.

Observation index: numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells.

60 cases with middle and advanced staged colorectal cancer were divided into 3 groups randomly. There were 20 cases in hyperthermia + TCM group, accepting Oncothermia in combination with TCM. Hyperthermia was applied 3 times a week, and orally taken herbal decoction was applied one dose per day, with the treatments for 2 months. There were 20 cases in hyperthermia group, accepting Oncothermia alone, 3 times a week, with the treatment for 2 months. There were 20 cases in TCM group, accepting herbal decoction alone, one dose per day, with the treatment for 2 months. Along with hyperthermia and TCM, all 3 groups accepted routine symptomatic supportive treatments, and there were no significant differences of symptomatic supportive treatments, age, gender, stage, and numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

5.1.1 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments

Table 1 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments ($\bar{x} \pm S$, %)

Groups	n	CD3 ⁺		CD4 ⁺		CD8 ⁺		NK	
		before treatments	after treatments	before treatments	after treatments	before treatments	after treatments	before treatments	after treatments
Hyperthermia + TCM group	20	31.20±5.	54.96±11.	24.18±2.1	39.96±3.0	40.08±5.3	30.97±2.4	16.14±1.5	26.37±1.0
	38		21*▲	7	5*▲	3	1*▲	2	6*▲
hyperthermia group	20	34.11±4.	47.31±3.2	23.94±3.0	34.10±2.9	41.26±4.6	36.22±2.6	15.29±1.5	20.18±1.5
	26		5*	1	7*	3	4*	4	3*
TCM group	20	32.42±4.	45.63±5.3	24.67±3.3	33.97±3.0	40.66±5.0	37.52±3.0	16.37±2.0	21.06±2.1
	03		3*	1	4*	2	1*	3	2*

* $P < 0.05$, after treatments, there were statistical differences of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

▲ $P < 0.05$, after treatments, the numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in hyperthermia + TCM group were statistically different from those in the other two groups.

5.1.2 Conclusions

This research showed that hyperthermia in combination with TCM could improve the immune function of patients diagnosed with middle and advanced staged colorectal cancer, and its therapeutic effect was better than hyperthermia alone or TCM alone ($P < 0.05$). Both hyperthermia alone and TCM alone could improve the immune functions of patients with middle and advanced staged colorectal cancer, but there was no significant difference between the improvements (the numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells after treatments) of the two groups ($P > 0.05$).

5.2 Effect of immunity of local hyperthermia in combination with Kang Lai Te Injection on patients with advanced cancer

Patient resource: inpatients of Clifford Hospital from July, 2011 to July, 2012 with advanced cancer.

Observation index: numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells.

45 patients with advanced cancer (8 patients with gastric cancer, 12 with colon cancer, 6 with lung cancer, 12 with breast cancer, and 7 with liver cancer) were divided into 3 groups randomly. There were 15 patients in hyperthermia + Kang Lai Te Injection group, accepting Oncothermia in combination with Kang Lai Te Injection treatments. Oncothermia was applied 3 times a week, with the treatment for 2 months. Kang Lai Te injection (Approval Number Z10970091) was applied 200mL per time through i.v., once per day, with 21 days as a course. After an interval of 3 ~ 5 days, the second course was applied. 2 courses of Kang Lai Te Injection were applied in total. There were 15 patients in hyperthermia group, accepting Oncothermia alone, 3 times a week, with the treatment for 2 months. There were 15 patients in Kang Lai Te Injection group, accepting Kang Lai Te Injection (Approval Number Z10970091) alone, 200mL per time through i.v., once per day, with 21 days as a course. After an interval of 3 ~ 5 days, the second course was applied. 2 courses of Kang Lai Te Injection were applied in total. Along with hyperthermia and Kang Lai Te Injection, all 3 groups accepted routine symptomatic supportive treatments, and there were no significant differences of symptomatic supportive treatments, age, gender, stage, and numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among 3 groups.

5.2.1 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments

Table 2 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments ($\bar{x} \pm S$, %)

Groups	n	CD3 ⁺		CD4 ⁺		CD8 ⁺		NK	
		before treatments	after treatments	before treatments	after treatments	before treatments	after treatments	before treatments	after treatments
Hyperthermia + Kang Lai Te Injection group	15	36.53±4.2	56.49±7.92	37.48±8.17	52.07±8.05	33.08±5.16	22.14±7.52*	15.14±6.84	25.47±5.91*▲
hyperthermia group	15	35.22±4.80	45.73±4.12	36.15±2.02	47.10±3.15	31.75±3.63	25.64±4.79*	16.13±3.26	21.15±2.93*
Kang Lai Te Injection group	15	37.64±3.0	46.91±2.33	34.43±4.13	44.96±7.62	33.17±9.02	23.68±8.72*	13.05±4.03	19.61±4.26*

* $P < 0.05$, after treatments, there were statistical differences of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

▲ $P < 0.05$, after treatments, the numbers of CD3⁺, CD4⁺, and NK cells in hyperthermia + Kang Lai Te Injection group were statistically different from those in the other two groups.

5.2.2 Conclusions

This research showed that hyperthermia in combination with Kang Lai Te Injection could improve the immune function of patients with advanced cancer, and its therapeutic effect was better than hyperthermia alone or Kang Lai Te Injection alone ($P < 0.05$). Both hyperthermia alone and Kang Lai Te Injection alone could improve the immune functions of patients with advanced cancer, but there was no significant difference between the improvements (the numbers of CD3⁺, CD4⁺, and NK cells after treatments) of the two groups ($P > 0.05$). In addition, there was no statistical difference among the numbers of CD8⁺ of the 3 groups after treatments ($P > 0.05$).

5.3 Effect of immunity of local hyperthermia in combination with Huang Qi Injection on patients with middle and advanced staged liver cancer

Patient resource: inpatient of Clifford Hospital from January, 2009 to May, 2010 diagnosed with middle and advanced staged liver cancer.

Observation index: numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells.

90 patients with middle and advanced staged liver cancer were divided into 3 groups randomly. There were 30 patients in hyperthermia + Huang Qi Injection group, accepting Oncothermia in combination with Huang Qi Injection treatments. Oncothermia was applied 3 times a week, with the treatment for 2 months. Huang Qi Injection (Approval Number Z51021776, with effective constituent of *radix astragali* 2g) was applied 20mL per time through i.v., once per day, with 20 days as a course. After an interval of 3~5 days, the second course was applied. 2 courses of Huang Qi Injection were applied in total. There were 30 patients in hyperthermia group, accepting Oncothermia alone, 3 times a week, with the treatment for 2 months. There were 30 patients in Huang Qi Injection group, accepting Huang Qi Injection (Approval Number Z51021776, with effective constituent of *radix astragali* 2g) alone, 20mL per time through i.v., once per day, with 20 days as a course. After intervals of 3~5 days, the second course was applied. 2 courses of Huang Qi Injection were applied in total. Along with hyperthermia and Huangqi Injection, all 3 groups accepted routine symptomatic supportive treatments, and there were no significant differences of symptomatic supportive treatments, age, gender, stage, and numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

5.3.1 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments

Table 3 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments ($\bar{x} \pm S$, %)

Groups	n	CD3 ⁺		CD4 ⁺		CD8 ⁺		NK	
		before treatments	after treatments	before treatments	after treatments	before treatments	after treatments	before treatments	after treatments
Hyperthermia + Huang Qi Injection group	30	47.63±5.17	59.08±6.98*▲	30.61±5.47	42.67±6.56*▲	28.79±4.66	24.64±5.30*	22.70±6.84	32.28±6.40*▲
hyperthermia group	30	44.82±7.83	51.73±6.74*	29.51±3.47	33.27±5.61*	29.08±6.43	26.01±5.07*	19.28±7.32	26.39±6.07*
Huang Qi Injection group	30	45.74±6.02	50.92±8.32*	27.60±7.81	34.06±6.69*	29.85±7.12	27.08±4.80	20.53±8.31	25.08±7.16*

* $P < 0.05$, after treatments, there were statistical differences of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

▲ $P < 0.05$, after treatments, the numbers of CD3⁺, CD4⁺, and NK cells in hyperthermia + Huang Qi Injection group were statistically different from those in the other two groups.

5.3.2 Conclusions

This research showed that hyperthermia in combination with Huang Qi Injection could improve the immune function of patients with middle and advanced staged liver cancer, and its therapeutic

effect was better than hyperthermia alone or Huang Qi Injection alone ($P < 0.05$). Both hyperthermia alone and Huang Qi Injection alone could improve the immune functions of patients with advanced cancer, but there was no significant difference between the improvements (the numbers of CD3⁺, CD4⁺, and NK cells after treatments) of the two groups ($P > 0.05$). In addition, there was no statistical difference among the numbers of CD8⁺ of the 3 groups after treatments ($P > 0.05$).

5.4 Effect of immunity of local hyperthermia in combination with acupuncture on patients with cancer after chemotherapy

Patient resource: inpatient of Clifford Hospital from October, 2012 to October, 2013 with cancer after chemotherapy.

Observation index: numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells.

60 patients with cancer after chemotherapy were divided into 3 groups randomly. There were 20 patients in hyperthermia + acupuncture group, accepting Oncothermia in combination with acupuncture treatments. Oncothermia was applied 3 times a week, with the treatment for 2 months. Acupuncture was applied once per day, with acupoints being selected based on differentiation of symptoms and signs, with 10 days as a course. There was an interval of 2~3 days after every course. 4 courses of acupuncture were applied in total. There were 20 patients in hyperthermia group, accepting Oncothermia alone, 3 times a week, with the treatment for 2 months. There were 20 patients in acupuncture group, accepting acupuncture alone, once per day, with acupoints being selected based on the differentiation of symptoms and signs, with 10 days as a course. There was an interval of 2~3 days after each course. 4 courses of acupuncture were applied in total. Along with hyperthermia and acupuncture, all 3 groups accepted routine symptomatic supportive treatments, and there were no significant differences of symptomatic supportive treatments, age, gender, stage, and numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

5.4.1 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments

Table 4 Changes of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells in 3 groups after treatments ($\bar{x} \pm S$, %)

Groups	n	CD3 ⁺		CD4 ⁺		CD8 ⁺		NK	
		before treatments	after treatments	before treatments	after treatments	before treatments	after treatments	before treatments	after treatments
Hyperthermia + acupuncture group	20	52.63±3.28	62.42±4.08 *▲	32.76±3.54	40.67±5.21 *▲	24.81±3.07	21.76±4.29*	19.90±8.65	30.74±8.97*▲
hyperthermia group	20	50.74±6.23	55.38±5.93 *	31.40±4.31	34.48±4.75 *	25.03±4.28	23.84±3.76	17.96±8.34	23.49±7.94*
acupuncture group	20	51.49±4.32	55.72±5.04 *	33.67±4.28	36.94±3.86 *	24.87±3.27	23.39±3.84	18.59±6.69	24.03±7.60*

* $P < 0.05$, after treatments, there were statistical differences of numbers of CD3⁺, CD4⁺, CD8⁺, and NK cells among the 3 groups.

▲ $P < 0.05$, after treatments, the numbers of CD3⁺, CD4⁺, and NK cells in hyperthermia + acupuncture group were statistically different from those in the other two groups.

5.4.2 Conclusions

This research showed that hyperthermia in combination with acupuncture could improve the immune function of patients with cancer after chemotherapy, and its therapeutic effect was better than hyperthermia alone or acupuncture alone ($P < 0.05$). Both hyperthermia alone and acupuncture alone could improve the immune functions of patients with advanced cancer, but there was no significant difference between the improvements (the numbers of CD3⁺, CD4⁺, and NK cells after treatments) of the two groups ($P > 0.05$). In addition, there was no statistical difference among the numbers of CD8⁺ of 3 groups after treatments ($P > 0.05$), and there was no statistical

difference of the numbers of CD8⁺ in both hyperthermia group and acupuncture group after treatments comparing to those before treatments($P>0.05$).

6. Effect of immunity of hyperthermia in combination with TCM in patients

According to the research data and reports mentioned above, in the clinical observations of Clifford Hospital, both hyperthermia and TCM treatment alone can improve the immunity of patients, which is also consistent with the reported clinical research progression. In addition, hyperthermia in combination with TCM (orally taken herbal decoction), anticancer Chinese formulated products (injection), and acupuncture all have positive immune regulating effects; and combined application has better therapeutic effects than applications of hyperthermia or TCM treatment alone. Based on this, we recommended this integrative treatment to other patients who didn't participate in our clinical research, and obtained positive therapeutic effect. In the future, we plan to do further research with bigger sample sized, stricter, double-blinded, randomized, and controlled trials, in order to obtain more clinical observations about immune regulating effect of hyperthermia in combination with TCM.

7. Prospects

Both hyperthermia and TCM have positive effects of immunity on cancer patients, and they play important roles in anticancer treatments. It is improved in both laboratory research and clinical research. The immune regulating effect of hyperthermia and TCM applied alone is widely admitted. According to clinical research in recent years at Clifford Hospital, as treatments which can improve immunity of patients, hyperthermia and TCM (herbs, Chinese formulated products, and acupuncture) have synergistic effect when applied in combination, and have great potentials in anticancer treatments.

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Oncothermia: New Method of Tumor Therapy

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Abstract

Oncothermia is a kind of hyperthermia in oncology. Its efficacy is successfully proven for different advanced cancer localizations, frequently when other therapies fail. Clinical studies and results show its advantages in oncology. Oncothermia is a self-selective process to concentrate the energy on malignant cells targeting their cellular membrane, using the temperature gradient to generate heat-flow between the extra- and intracellular electrolytes, acting to ignite apoptotic processes from outer signal-pathways. Synergies of oncothermia with some chemotherapy were observed, having more efficacy than in the conventional heating combinations. Experiments and clinical results showed the higher benefit of the oncothermia when compare with the results of classical hyperthermia activity at same level of temperature. This paper will review the literature and illustrates the difference between oncothermia and hyperthermia treatment. It will also highlight the effectiveness of oncothermia treatment for different types of tumor. Oncothermia is widely used in numerous clinics and hospitals enjoying definite clinical benefit on elongation of the survival time accompanied with good quality of life.

Keywords: Oncothermia, clinical applications, clinical studied cancer, tumor, hyperthermia, electric-field, electromagnetic radiation, electromagnetic field.

Introduction

Hyperthermia is an age old therapy which originated from Egypt. This age old tradition has been revived by the discovery of electromagnetic energy without causing significant toxicity, absorption of electromagnetic energy directly or indirectly promotes tumor destruction with different favorable physiological and cellular effects. Oncological hyperthermia is the combination therapy, providing synergistic effects with most of classical treatments. Recent books on radiology and oncology have dedicated a part of its topic on hyperthermia, with no surprise there are large number of books discussing this, it's also be discussed and referred in different books and high-ranked clinical journals. [1, 2].

In medical literature hyperthermia has varieties of definition which all involves high temperature and differ only in localization which ranged from cellular to whole body heating. Hyperthermia is involves over heating of a particular affected tissue [3,4].

Hyperthermia involves energy transfer mechanism which regulates and causes changes in the energy flowing in the tumor region. The modern conventional traditional oncological hyperthermia methods [1] use non-ionizing electromagnetic radiation [3]. The changes, however, could have both the directions, the accelerated growth and promoted dissemination is also an option together with the opposite: to suppress of the tumor growth, destroy the malignant cells. Due to the opposite possibilities the method and the technique of the energy-transfer have crucial role.

The controversial results of the causes of hyperthermia therapy is technically challenging the deep heating to medical and technical personals [6,7]. How deep-seated tumors can affected by energy? Selection between malignant and non-malignant normal areas? How to enhance the effect of hyperthermia on malignant area and avoid changes in normal areas? How to reduce or prevent irritation / toxicity to normal cells? How to produce reproducible dose and control the medical treatment? The answers are delivered by oncothermia.

Oncothermia had formulated a new paradigm, [4] trying to make it clear "What is against the acceptance of hyperthermia?" [5]. It is no question: hyperthermia is a thermal medicine. The heating, the energy absorption in the living tissue and in consequence the rise of its temperature is the basic mechanism of hyperthermia. Oncothermia is definitely hyperthermia, it uses thermal

effects in its action. The temperature in nano-ranges could be even higher than what the local non-invasive hyperthermia methods usually produce.

Oncothermia [6], is a kind of oncologic hyperthermia using well selective electromagnetic effect [7] for the cancer-cells. Oncothermia adopts low-radio frequency to modulates the electromagnetic effect of the methods of traditional oncology with significant applications [8].

Preclinical Studies

Using specific difference among the tumor cells and healthy cells, oncothermia overcomes all the challenges posed by hyperthermia in oncology [9], by using electromagnetic way [10]:

1. Applying mechanism like self selective in which current goes self-selectively only to the affected malignant cells (in this case the focus would be automatic). [11].
2. The method of oncothermia modifies the distribution of energy, to optimize the selective distribution and avoids the homogeneous heating of the area. It targets the cell membranes by affecting the extra-cellular matrix and heating up their electrolyte thus initiate heat flow from extra-to intra-cellular compartments through the membrane becomes more transparent, and destroyed [12].

These points are realized, and this procedure is called modulated electro-hyperthermia or oncothermia [13]. Oncothermia was designed after considering many theoretical considerations for idea work. Application of oncothermia is also supported by fractal-physiology) studies or fluctuation analysis. [14].

To understand the effect of oncothermia alone and compared with traditional methods of heating some preclinical experiments has been conducted. The experimental setup allowed maintaining conditions identical for both methods of heating, heating in conventional manner and in the form of oncothermia. Oncothermia experiments (in-vivo and in-vitro) were performed by a laboratory device specially developed for such purposes.

Oncothermia is a selective process in which the extracellular matrix of the cancerous tissue has higher conductivity and allows radiation [15]. It is well documented in the literature [18] that oncothermia selectively destroys the malignant melanoma cells (A431 cell line) without affecting the normal fibroblast. [16].

The changes in heat transport across plasma membrane induce bobbling and distortion in the membrane [12]. These are high efficacy factors favoring oncothermia over its temperature-equivalent hyperthermia counterpart.

The setup was configured to provide fine temperature control, which is responsible for heating, maintaining the temperature and dynamic cooling. Temperature changes lead to induction of shock protein. The characterization by the temperature like average was validated by luciferase transient transfected HEK293 cell lines [17].

The broken adherent connections (E-cadherin and β -catenin) could be reestablished by oncothermia allowing the “social signals” and so promoting the apoptosis [18].

In the study of effect of oncothermia in human hepatocellular carcinoma (HepG2 cellline), a significant changes in dynamic development of beta-catenin was observed after 24 hours of the treatment [19]. Apoptosis is an indicator of the sudden regrouping of beta-catenin and its enrichment in the cell nucleus [21]. Proteins conditions of apoptosis induction by the external signal are shown in the mRNA level [22] and in protein level [23].

It has been shown, that the apoptotic process by excitation of the cytoplasmic membrane is caspase independent in majority [19], and the upregulation of death receptor TRAIL-R2 (DR5) together with FAS and FADD proteins has definite role in it [20]. AIF nuclear translocalization was observed at 14-24h, which again well corresponds with the caspase-independent signal transduction [21]. The mitochondrial pore formation (BAX) was associated with cytochrome C release, which is generally the “point of no return” of the apoptotic process [22]. The DNA fragmentation of late apoptotic process was obviously shown by a massive TUNEL positivity developed at 24-48h post-treatment.

At the same temperature in hyperthermia necrosis is preferred whereas in oncothermia apoptosis was more likely as observed by detecting double strand of DNA (DAP) staining and by measuring the enzymatic labeled strand break of DNA (TUNEL- FICT). The results indicate that in-vivo and in-vitro correlation. The outstanding tumor targeting can be proven by the temperature measurement in the cancerous and the neighboring tissues.

In vivo effect was proved by the Xenograft tumor-models. The model was obtained by inoculation of Human colorectal carcinoma cell-line (HT-29) subcutaneously, into the thigh region of nude mice with 6×10^6 cells into the thigh of nude mice. 18 Days after the tumor inoculation the experiments were conducted. Animals which developed tumors symmetrically and of approximately the same size were included in the study.

Local classical hyperthermia and oncothermia were used in the study. Fluoro-optical method was used to control and accurately measure intra-tumoral temperature.

Mortality rate after treatment was calculated by morphological criteria comparing the different modalities of treatment on basis of pathological changes and by distinguishing area of intensive proliferation from other areas showing necrotic, dead cells. Changes in tumor area of animals that of control and treated regions were compared and analyzed statistically. Statistical significant difference was observed. (Fig. 1).

Figure 2 depicts the comparison and histological evaluation of hyperthermia and oncothermia combined both methods with mitomycin-c (MMC) single dose chemotherapy in vivo at tissue and cellular level. Nude mice having HT29 human colorectal carcinoma cell line derived xenograft tumor model was used. Animals (2 each) of hyperthermia (42°C) and oncothermia (42 °C) were treated with 3 mg/kg mitomycin-C (half an hour prior the treatment).

The effect of temperature was investigated [23]. The same temperature application of the two thermal treatments was tried together with the only field application (cooled back) case (Fig. 4.). Figure 4 indicated the advantage of oncothermia where the electric field has significantly higher synergistic effect on cell-killing process (Fig. 4) .

Clinical studies

Oncothermia is a method realizing the above effects in personalized manner [24], utilizing the energy liberation and consequent heating at the immediate vicinity of the outer cell-membrane of the tumor cells. Numerous in-silico, in-vitro, in-vivo and preclinical experiments take precedence of the clinical applications, and the method is in fact applied worldwide [25]. Several clinical studies are reported which shows the efficacy of hyperthermia in oncology. Interesting results were observed with the irradiative as well as with capacitive hyperthermia, with some serious troubles.

In year 2000, what seems a breakthrough was recorded [26] in cervical carcinoma, which is a serious condition, using combination of hyperthermia with radiotherapy. But, later the results could not be reproduced [27]. The optimum temperature required for activity could not be optimized [28]. The definite problem is always to find optimum energy required for targeting and treating the tumor [31, 32].

The efficacy of hyperthermia in oncology was shown in results of many clinical studies, but the drawback in some of these studies are shown in difficulties of comparing with controls and sometimes the unrepeatability as mentioned cancerous clinical studies of carcinoma of cervix [29] [30]) [31].

Oncothermia can be applied in cases when conventional heating has definite complications or even contraindication. These are the near-eye applications, the bleeding, inflammatory cases and the sensitive organs (like brain) in advanced conditions (like large intracranial pressure). There are multiple case reports showing unique possibilities of oncothermia in these cases above. For example, the case of a 67 years old patient who had an inoperable squamous epithelium carcinoma in sphenoidalis sinus causing right opthalmology, treated with radiation and oncothermia. The results is a complete remission of the tumors. This is a case of near eye application [32].

Another example: a case report of a male patient of 54 years with carcinoma of esophagus carcinoma, treated with chemotherapy, surgery 50Gy-radiotherapy were not effective, the condition progressed to dysphagia (blocking the food-passage), Then treated with 6 oncothermia [33]. The condition showed improvement and then, after 12 treatments there was complete regression of the tumor.

Several research papers and clinical data published indicates the utility of oncothermia. In retrospective, study of results of using oncothermia in human, including reviews and research papers, most of these studies were single arm, open label studies for treating people suffering from advanced stages, where the traditional methods of treatment had failed. It includes inoperable and progressive malignancies after fasted chemo- and radiotherapies. Exclusions were only the well-known contraindications of hyperthermia: after organ-transplant (due to the massive immune-suppression), pregnancy, missing communication ability, missing temperature sensing on the treated area, etc. High attention and exclusive care is necessary in cases of electric implants (like peacemaker) or large metallic implants (like hip-replacement or skull-cover), patients with epilepsy, with high sensitivity for electric fields or other personal problems or comorbidities.

Some case show erythema (<8%), at site of treatment but no subcutaneous toxicity or other side effects, when there is a conventional treatments (radiotherapy and/or chemotherapy), patients show the usual toxic effect. Most patients reported less pain than before with feeling of being better

In the retrospective studies of collection of cases one obvious negative drawback appear, that is the lack of controls and there is a bias in selection of cases according to voluntary decisions. In these studies the end points were to compare the survival rate to be compared with conventional treatments.

The treatments were made on a voluntary basis for ITT population, which was negative bias as well. Positive bias was the selected very advanced patient-population. Also positive is the missing “trial psycho-attention” and the entirely regular treatment conditions (no extra care is given). The primary endpoints of the studies were always the survival rate, which was evaluated by regular descriptive biostatistics and log-rank survival test.

Most cases that were included in studies using oncothermia in treatment of brain, lung, liver, pancreas, g.i.t, vaginal and testicular tumors and these form a vast data. The retrospective data are compared to the large databases (Seer [34] and Eurocare [35]), having possibility to see the position to the best available data in a huge average.

The clinical studies of oncothermia cover various lesions [25]. Average number of patients in the studies is 53, by lesions 116. Maximal patient number in a study (Phase III) was 311 (NSCLC) [36]. The average oncothermia enhancement ratio (ratio of the median survival of responders to non-responders) was 5.1. Some special results are published for gliomas [37, 38, 39, 40, 41]; for hepatocellular carcinoma (HCC) [42]; for liver, (metastatic of colorectal origin) [43, 44]; for bone metastasis from NSCLC [45]; for pancreas [46, 47]; for cervix [48], for ovary [49]; for prostate [50], for soft-tissue sarcoma [51], for biliary carcinoma [52]. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.

Though the survival rate of cases treated by oncothermia is very low but still this is better than the classical treatments. Mostly oncothermia was applied after failure of other treatments. The efficacy of oncothermia is indicated, when it has some benefit in cases where the disease is aggressive with short survival. For these reasons Szasz and Dani, have compared the 1st year survival rate only (see Fig 5). In this sense oncothermia is indicated as a feasible, effective method [53].

The median of overall survival time is also gained in most of the localizations despite of the only advanced cases in oncothermia treatments, (Table 1.).

Studies of using oncothermias in brain tumors specially in brain-gliomas were reported in papers presented in Conferences like ASCO [54], ICACT [55], ESHO [56], ICHS [57], ICHO [58], and others [40, 59]. The results seem to indicate a significantly higher survival rates in comparisons with other treatment and also age-adjusted survival is higher.

Oncothermia is found to be exceptionally good in the complicated situations, which arose due to cooling of large blood flow and chemo-toxicity from previous treatments in metastatic liver tumors. Published results indicates that oncothermia is exceptionally good for colorectal liver metastasis as well [40, 60, 61, 62].

Concerning liver tumors, oncothermia was not expected to be very effective due to complicated situation and cooling of large blood flow through it but experimental studies on condition o colorectal metastasis to the liver indicated that oncothermia was successful.

The sensitivity of the liver during chemotherapy in advanced cases (if other treatments were unsuccessful chemotherapy) is well observed in the combination therapy compared to single Oncothermia. [67]. When chemotherapy was combined with oncothermia, it gives a better response that it is used as a single treatment. [62]

The same results were reported concerning carcinoma of pancreas, reports presented at ASCO [63] and other conferences [64, 65, 66] indicated that oncothermia improved the results when combined with conventional treatments. The statistical significance was clearly shown by comparing the results of six different clinics in two countries studying the same cancer having the same cohort with the same protocol. Their definite agreement and deviation from the general databases offer statistical evidence. In spite of that the lung is a complicated organ and has a cooling effect due to ventilation of breathing, but oncothermia was proved to be effective as a treatment for lung cancer, that is due to non-equilibrium features of the treatment [60, 66].

Presently oncothermia has installations in 30 countries on five continents providing at least 200.000 treatments in a single year in numerous small medical offices and in large university clinics, too. Oncothermia has altogether 62 clinical up-to-date studies, involving 3790 patients from five countries (Germany, Hungary, Italy, S. Korea, and China). Further clinical trials are in progress for advanced ovarian, breast, pancreas, liver, colorectal and esophagus cancers, in many countries like Germany, Italy, China, S. Korea, S. Africa, and Japan. Multiple clinical and preclinical studies are in progress in various university research centers, too.

Conclusion

The war against cancer [67] had not been finished yet. There are multiple excellent clinical results of the local control of the solid tumors, but the survival time is far not well impressive. Many patients fail to respond to the conventional “gold standard” therapies, and have advanced cases, many times forming terminal stage after multiple treatments. No curative treatment exists for these cases, only palliation helps for a short time; the first goal is to provide acceptable quality of life which is an important factor for oncothermia, too. Oncothermia is devoted to offer curative treatment for patients as the facility of the “no other is possible”, for patients in “hopeless cases” providing over 3rd line treatment approach. However, oncothermia has curative value even in these advanced situations, and makes curative therapy in 3rd-line or over. The professional literature clearly shows the rare facility of the evidence-based clinical trials for these high-line treatments. Other evidences have to be shown when randomized controlled trials are not possible [68]. The challenges of evaluation appear forcefully in case of patients with advanced stages, having inoperable (or partly resected) tumors, having relapsed malignancies, patients who are resistant to the gold-standard treatments, etc. Oncothermia is facing to this challenge as well. Efficacy of oncothermia is shown by multiple curative cases with detailed case reports. Oncothermia is a new, nano-heating hyperthermia method in oncology. It has good clinical achievements in the far-advanced clinical cases, studies, making stable basis of the clinical applications in various advanced primary and metastatic malignancies.

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Table 1. Comparison of median SEER and Oncothermia of overall survival-times

#	Tumor location	Patient No		Overall Survival	
		SEER	Oncothermia	SEER Median	Oncothermia Median
1	Brain glioma	2897	157	11.49	22.4
2	Colo-rectal	242920	295	45.60	27.6
3	Esophagus	18302	17	9.07	29.37
4	Ovary	39383	27	31.78	37.83
5	Corpus Uteri	68271	9	1264	61.5
6	Kidney	38270	52	51.92	36.1
7	Liver	12696	39	7.33	19.8
8	Lung	268106	275	965	16.2
9	Pancreas	47368	124	7.25	12.4
10	Soft-tissue	11256	26	88.88	35.1
11	Stomach	42813	81	10.24	14.7
12	Prostate	243451	18	83.09	38.78

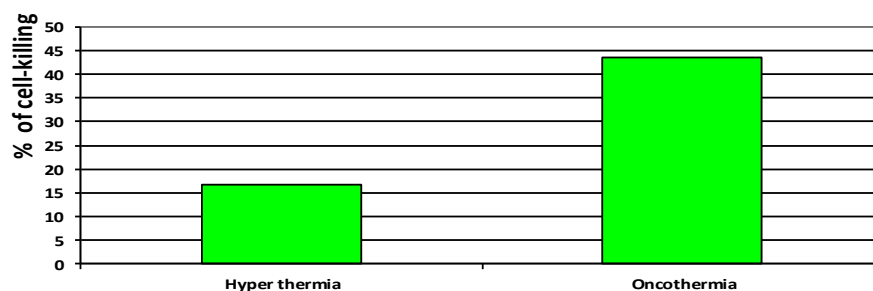


Fig. 1. The macro-evaluation of the efficacy of oncothermia in comparison to the hyperthermia in HT29 tumor xenograft. Change of the areas of dead and vivid parts in percentage of the untreated control on the same experimental animal (data average of 3 animals each). Similar experiments were carried out with the same results for A431 human epidermoid carcinoma xenograft model and GL261 murine glioblastoma model.

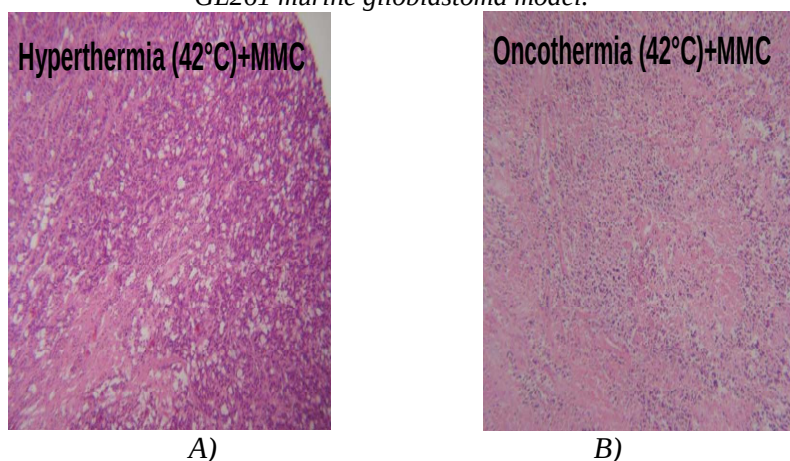


Fig. 2: Investigating the difference of the effects of i.p. administered Mitomycin-C. A). The cell-killing Ais relative to the control tumor on the same animal. (Two-two animals were measured with double tumors on each for control.) B) Hematoxilin-eosin stained microscopic images of tumor samples.

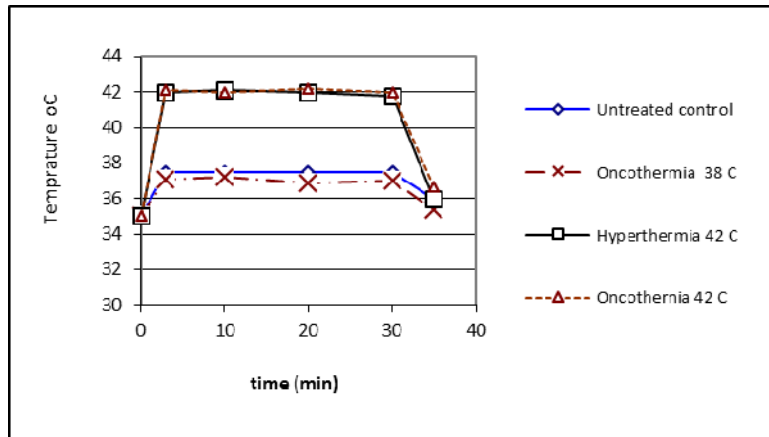


Fig. 3. A sample of the temperature pattern of hyperthermia and oncothermia (at diff. temperature)

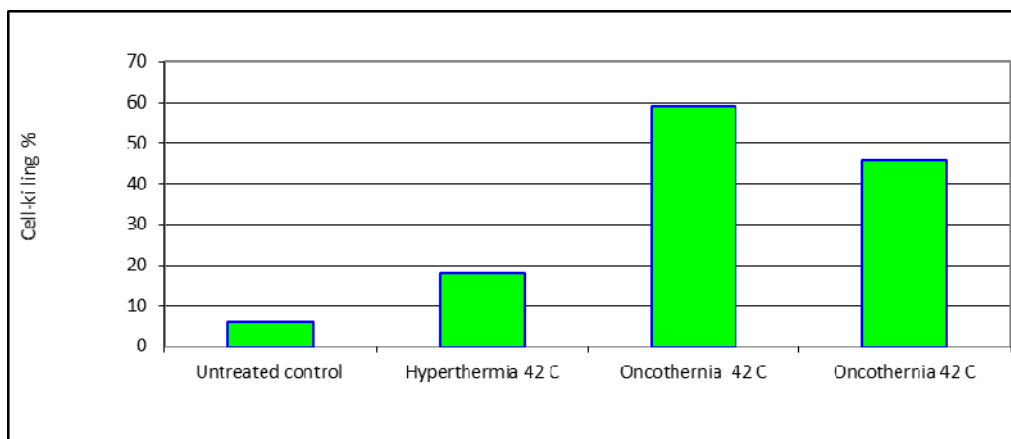


Fig. 4. Comparison of percentage of cell-killing of hyperthermia and oncothermia at different temperatures.

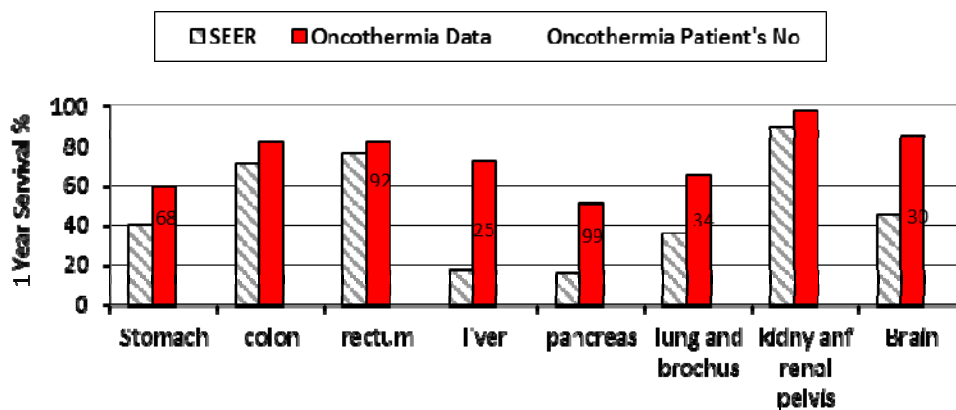


Fig. 5. Comparison of the first-year survival rates of various cancers with the large databases. Improvement of the first-year survival percentages of oncothermia (advanced patients) compared to SEER and Eurocare data weighted average. No of patients of various cancer group are written on each column.

**Case reports from Oncothermia Clinic. Early experiences.
Karachi, Pakistan**

Saima Zahoor*, Unsa Mohsin*

* Oncothermia Clinic, Karachi, Pakistan

Patient 1

78 y old female, Pakistani

Background – Patient felt a lump on her right breast 7 year ago. It was firm to hard measuring around 6x5cm and there was no significant change in size for next 4 years. Patient did not visit any hospital, after 4 years lump started increasing in size along with some pain in that region. Patient was not willing for any treatment but around 6 months back when patient had severe pain in region she had biopsy done showing invasive ductal carcinoma, ER (+), PR (+). Surgery was done in January 2016, (MRM). Her breast was inflammatory with open wound, fig. 5. The patient refused chemotherapy after surgery, after 2 months patient noticed another lump in her left breast along with bloody discharge from the site around aerola (L) there was fungating wound 7x9cm with irregular margin. Bloody discharge was from right sided scar mark, too. She was generally weak, she had severe pain in hip joint that unable to walk without support. Her active complaints are nausea, heart burn and vomiting.



Fig. 5. Patient's breast before treatment

Diagnosis (2016) – Stage IV invasive ductal cancer of the breast (Left) with multiple metastases, spreading to lung, spleen, skin of right chest wall, bone and lymph nodes. The patient nutritional state was average, her breast was ulcerated with infection. She was unable to walk because of her poor health and decreased appetite. First the patient was given antibiotic cover for the sores on the breast.

Treatment – Patient was given Oncothermia (10 sessions) complementary to low dose chemotherapy. Chemotherapy was 6 cycles of Inj. Taxotere with standard protocol. Oncothermia was given twice weekly for 1 hour session. Nutritional support (minerals and vitamins) was also given in the form of injectables.

Results – After 45 days' nontoxic integrative cancer treatment using Oncothermia and complementary chemotherapy the sores of the breast and scar tissue were remarkably better and at the end it is completely healed, Fig. 6.



Fig. 6. Patient's breast after treatment

Radiological examination of chest and abdomen revealed that breast and skin soft tissue thickening and degree of enhancement were markedly decreased especially breast (L) thickening decreased from 9.0mm to 2.4mm. Multiple growth in lung, spleen have shrunk, no new growth were detected. Hilar and mediastinal lymph nodes also decreased in size, HB 11.1gld, Pt 192,000 per cum, Urea 24mg/dl, Creatinine 0.67mg/dl, WBC 6,700 per cum. Patient's health status, quality of life have very much improved that her pain and generalized weakness have been resolved and she can walk even without support. Now she is on her maintenance dose for Oncothermia twice a month.

Patient 2

46 y old male, Pakistani

Background –The status of the patient was post right-nephrectomy and post radiotherapy. Patient was in bad health status, his score of quality of life was low. He was pale looking, mentally he was not alert, lethargic, having deep depression. His appetite was weak, he had remarkable weight-loss, he was unable to carry out his routine work.

Diagnosis (2016) – Patient was diagnosed of renal carcinoma in 2015. He developed bilateral lung metastases detected with PET scan. Size of the largest metastasis was 3.3x3.1cm in posterior basal segment of left lower lobe, and metastatic deposit of 1.2cm was also detected in right adrenal region. Few reactive metastatic lymph nodes were in aortocaval region as well.

Treatment – Oncothermia was provided for the patient from 2-08-2016 to 6-09-2016 after 10 sessions of Oncothermia + Chemotherapy (Tab: Affinit every other day).

Results – Pulmonary metastatic deposits of the patient reduced remarkably from 3.3x3.2cm to 1.8x1.5cm in posterior basal segment of left lower lobe of lung. His right adrenal metastatic deposit was completely resolved from 1.2cm, reactive/metastatic lymph nodes in aortocaval region were completely resolved, too. Patient's quality of life remarkably improved. He gained weight, his appetite increased, his depression weakened, he was alert and even he started driving a car. Now patient is in follow-up and controlled frequently in every 10 days.

Advertisement

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Prio mensch
Privatpraxis für Integrative
Onkologie
Cologne, Germany

„Das Ziel von prio mensch ist es, den Patienten mit all seinen Facetten zu sehen und seiner Individualität, gerade in Zeiten der Krankheit, durch eine ganzheitliche Behandlung gerecht zu werden.“

So beschreibt Dr. Birgit Stolze, die seit diesem Jahr auch mit einem Oncotherm-Gerät arbeitet, die Grundidee ihrer Praxis in Köln.

Als Fachärztin für Innere Medizin, Internistische Onkologie und Hämatologie und Bluttransfusionswesen hat Dr. Stolze ein Team um sich gebildet, das jedem Patienten Hand in Hand und an einem geschützten Ort die beste und umfassendste Behandlung bieten kann.

Dass der Patient und sein Wohlbefinden bei prio mensch im Mittelpunkt stehen, spürt man in jedem der modern eingerichteten und in warmen Farben gehaltenen Behandlungsräume. Die Praxis ist zentral gelegen, so dass jeglicher Anreisestress entfällt. Mit dem Aufzug gelangt man in den sechsten Stock und wird von einem freundlichen Team in Empfang genommen, ohne großen Patientenströmen ausgesetzt zu sein. Denn gerade in Zeiten der Krankheit ist es wichtig, sich in seiner Würde ernstgenommen zu fühlen und die Sicherheit zu haben, in guten Händen zu sein.

In der Integrativen Onkologie werden die klassisch-schulmedizinischen Methoden wie Chemotherapie und Antikörpertherapie mit sinnvollen, komplementären Behandlungsformen wie lokaler Tiefenhyperthermie und Misteltherapie kombiniert. Dadurch erfährt der Patient die maximale medizinische Unterstützung in jeder seiner Behandlungsphasen.

In enger Absprache mit dem Patienten erstellt Dr. Stolze einen individuellen Behandlungsplan, der auch Gestalt-, Kunst- und Musiktherapie, Ernährungsberatung sowie psychoonkologische Begleitung innerhalb der Praxisräume mit einbezieht.

Das Behandlungsangebot von prio mensch beinhaltet folgende Therapien:

Integrative Onkologie

Chemotherapie

Immuntherapie

Transfusionen

Misteltherapie

Lokale Hyperthermie

Psychoonkologie

Palliativmedizin



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nach Dr. Rilling

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Diagnostik in Zahlen –
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Das Biotonometer® ermöglicht es Ihnen,
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die aktuelle vegetative Ausgangslage Ihres
Patienten zu bekommen.

Mit der Zeit gehen, Krankheit messen!
Der Zeit voraus sein, Heilung beweisen!

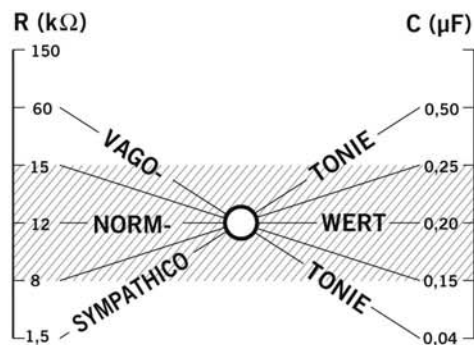
Anwendungsgebiete:

- Analyse des Gesundheitszustandes Ihres Patienten
über die vegetative Ausgangslage
- Medikamententest über Solarplexus
- Nahrungsmittelunverträglichkeitsmessung
- Therapiekontrolle
- In vitro Messung von Medikamenten und
homöopathischen Mittel

Gern informieren wir Sie über die Anwendung
und den günstigen Erwerb des Gerätes.



Waagebalkenprinzip nach Dr. Rilling



Die Funktion des Parasympathikus entspricht dem
 $R = \text{Widerstandswert in } k\Omega$.

Normwerte Parasympathikus: $\geq 8 \Omega - \geq 15 K\Omega$

Die Funktion des Sympathikus entspricht dem
 $C = \text{Kapazitätswert in } \mu F$.

Normwerte Sympathikus: $\geq 015 \mu F - \geq 0,25 \mu F$

Werte außerhalb dieser Grenzen deuten
auf eine vegetative Dysfunktion hin.

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Oncothermie in den Gebieten Berlin, sowie
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Ganzkörperhyperthermie sowie unser weiteren Leistungen bieten wir in
der gesamten EU bzw. den USA an.

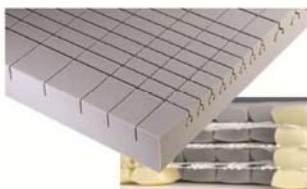
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Akutflegebetten, Transportliegen und –Stühle die durch Funktionalität, Langlebigkeit und Design auffallen. Benutzerfreundlichkeit, Komfort und Hygiene stehen im Vordergrund. Einsatz bis zu einem Arbeitsgewicht von 500 kg.

Pflegebetten, die PatientInnen neben ausgeklügelter Technik ein „Woh(l)gefühl“ vermitteln. Robust, funktionell und komfortabel mit hochwertigem Design; wie maßgeschneidert für den individuellen Bedarf in vielerlei Leistungsklassen verfügbar.



Lagerungssysteme vom Grundbedarf bis zum 350 kg Patienten bis Stadium IV (nach EPUAP). In puncto Druckentlastung und Mikroklima dürfen Sie mit fünfzig Jahren Erfahrung und Spitzenwerten rechnen.



Krankeneinrichtung, die nicht nur praktisch ist, sondern auch imagefördernd sein kann. Der erste Eindruck ist oft der intensivste, zeugt doch die Einrichtung auch von der Wertschätzung, die der Klinikbetreiber PatientInnen entgegenbringt.

Ihr Partner in Sachen Lagerungssysteme, Klinikeinrichtung, Hyperthermie, Patientenmonitoring und Ultraschall Diagnostik
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Oncothermie kombiniert Hyperthermie mit einem elektrischen Feld. Durch diese Synergie kann die Methode noch schonender bessere Ergebnisse in der Krebsbekämpfung erzielen.



Monitoring Patientenüberwachung steht ganz vorne. Stand-alone oder im Netzwerk, konfiguriert, modular oder telemetrisch. Ausdrucke oder KIS-Anbindung. Sie haben es im Blick. Wählen Sie im modularen Bereich auch unter Sonderparametern wie Relaxografie, Entropie, BIS oder Stressmessung. Die Geräte unterschiedlicher Leistungsklassen sind untereinander kompatibel, so dass auch die Umsetzung komplexer Netzwerke kein Problem darstellt.

TOP NEUHEIT



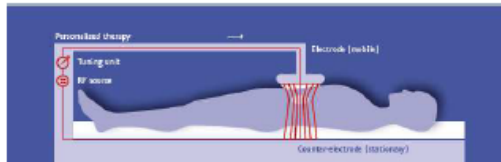
Blasenscanner Der HD 5 kann unnötige Katheterisierungen, Infekte, Überdehnungen und Rückstauungen vermeiden helfen. Online scannend und mit Blasenwandmarkierung ausgestattet, kann der weltweit flachste Blasenscanner kinderleicht bedient werden. Akku gestützt, aber auch mit Netzstromversorgung benutzen Sie das Gerät komfortabel auf seinem Fahrgestell mit Dockingstation. Sicher-Genau-Zuverlässig. Gut für PatientInnen, Pflegepersonal und Wirtschaftsabteilungen.

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Information

Oncothermia-Method & Oncotherm-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, that is generated by two active electrodes.

EHY-3000 series

The EHY-3000 series is designed for the simultaneous multi-local treatment of advanced, metastatic disseminated, malignant and solid tumors. Within the range of Oncothermia systems, it is the pioneering breakthrough in the field of multi-local tumor therapy. Due to its highly flexible application electrodes (textile electrodes), almost all tumor locations can be treated.

EHY-2000 series

The EHY-2000 series, including EHY-2000 plus and EHY-2010, is the classic system for locoregional deep Hyperthermia applications. This series has been used for treatment throughout the world for more than 20 years. The EHY-2010 has been specially developed for practices and hospitals that have little available space but do not want to do without the classic treatment.

EHY-1000 series

The EHY-1000 series is our newest development in the treatment of prostate diseases. Both malignant and benign tumors (BPH) can be treated using a catheter system with built-in electrode and counter electrode.

Booster

The Booster is a product innovation in the field of complementary treatments. Its use enhances the effects of drug treatment and it can be applied in various medical fields.

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