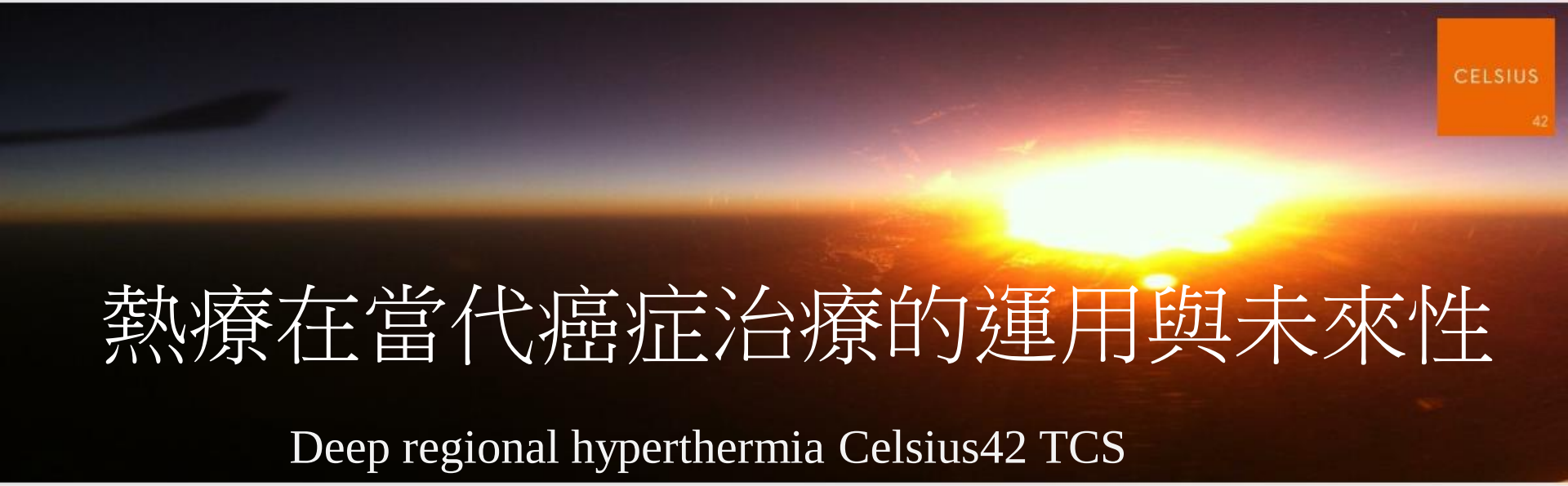


熱療在當代癌症治療的運用與未來性

Deep regional hyperthermia Celsius42 TCS

Part II: The Rationale of Hyperthermia

Presentation by Dr. Michael Chen
陳智良 醫師

March 2020, modified from D. Martin Roesch

陳智良 醫師

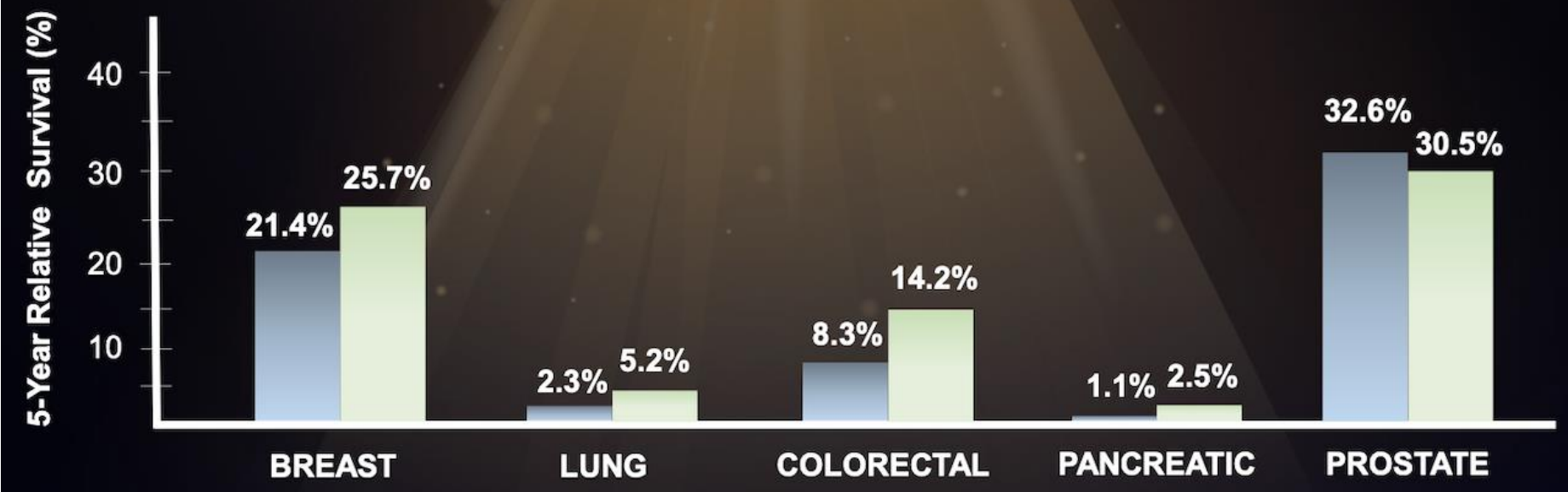
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- 外科專科醫師
- 消化系外科專科醫師
- 乳房專科醫師
- 針灸專科醫師
- 國軍高雄總醫院一般外科
- 高雄長庚醫院一般外科
- 德國熱療學會(DGHT)會員
- 瑞士生物性醫學(Swiss Biological Medicine Academy)認證
- 三一診所(高雄) 院長
- 維君良耀診所(竹北）
- 整合性癌症療法
- 粒線體療法

- 全身性熱療,water-filtered IRA whole body hyperthermia,Von Ardenne Institute, IRATherm1000
- 深度局部性熱療,Deep regional hyperthermia, Celsius42 GmbH: Celsius42 TCS
- 光動力療法(Photodynamic therapy, PDT), Weber medical GmbH
- 電磁脈衝(PEMF), Papimi Europe
- Apurano Pharmaceuticals GmbH, CuraXan2(薑黃素之臨床研究)
- Prof. George Birkmayer NADH

Only Marginal Improvement in Metastatic Cancer Survival Rates over a 20-Year Period

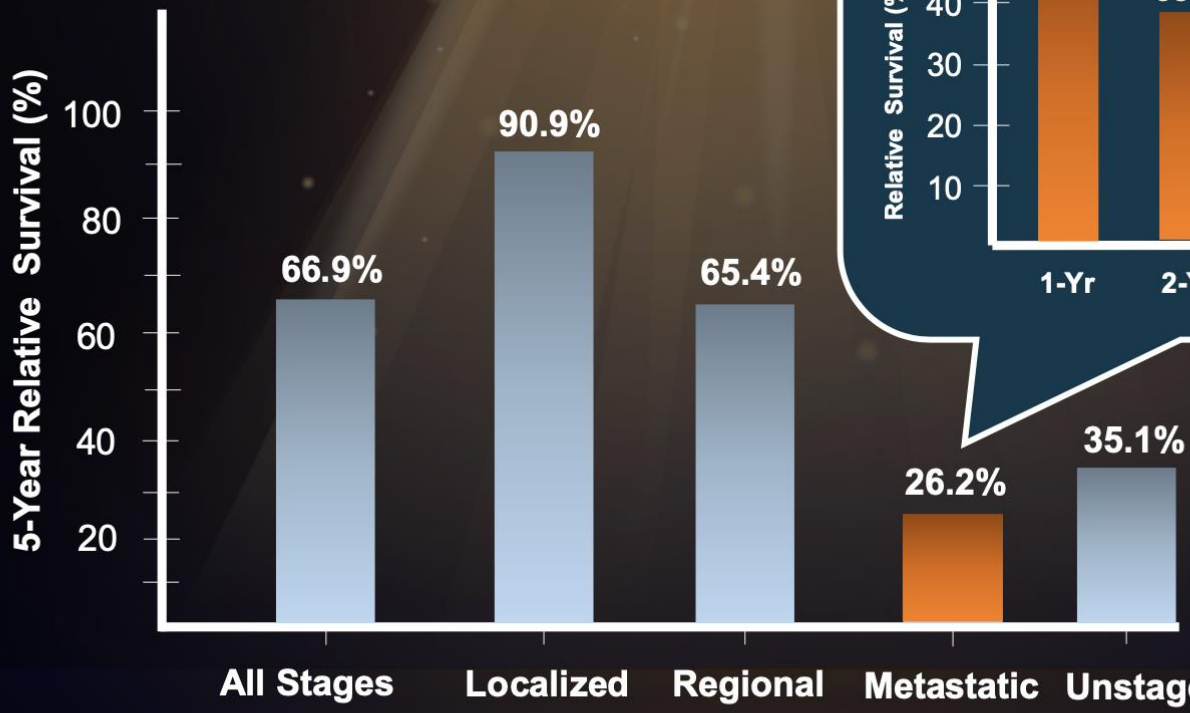


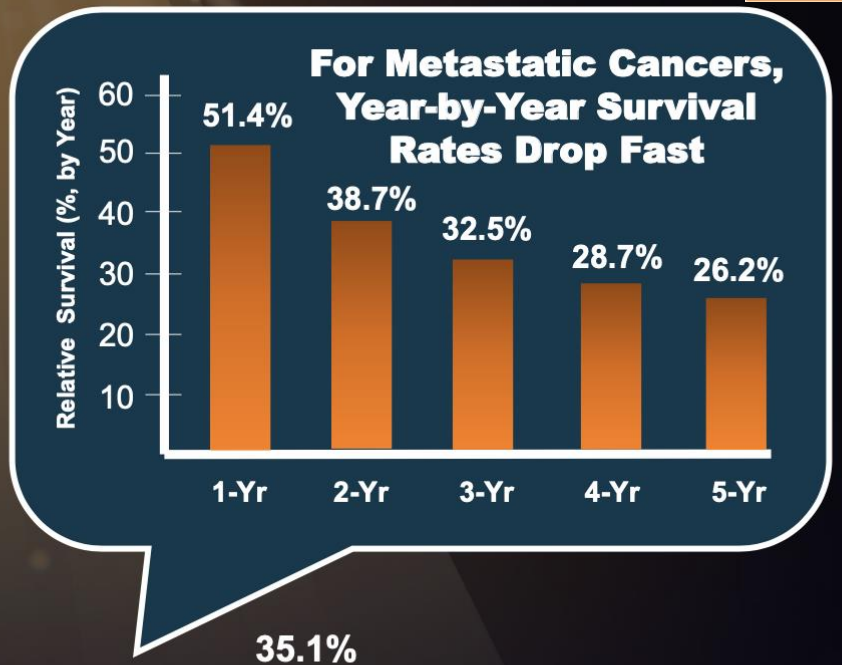
5-Year Relative Survival for Metastatic Cancer

SEER Data (1989-1994) vs. SEER Data (2008-2014)

5-YEAR RELATIVE SURVIVAL FOR ALL CANCER SITES BY STAGE

(2008 – 2014 SEER Data, USA)





SEER 18, Relative Survival by Stage (2008-2014 Data)
Cancer Query Systems: SEER Survival Statistics

We are facing stagnation for the metastatic cancerous therapy either in

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- Radiation
- Chemotherapy
- Surgery
- Targeted therapy
- Immunotherapy

What can we do?

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⇒ Improving the quality of life

⇒ Increase in response rates

⇒ Extension of survival rate, Cure??

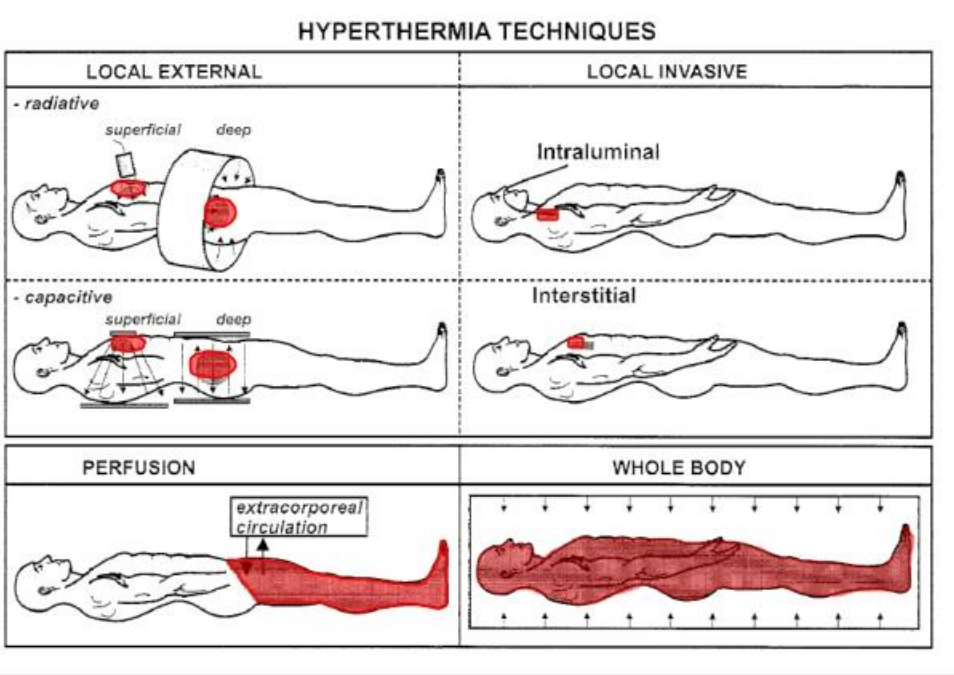
Can hyperthermia therapy do something for this dilemma?

⇒ Extension of survival u. Cure??

Hyperthermia forms & methods:

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I. Active hyperthermia (fever inducing, medical drugs, viral therapy, mistel)



Kodata Consensus Conference, 2004

II. Passive hyperthermia (device)

A. Whole Body Hyperthermia (WBH)

*** Mild (-39 °C)**
*** Moderate (39-40,5 °C)**
*** Extreme (41-42,8 °C)**
*** Thermotherapy (~ 43°C, 15 min.)**

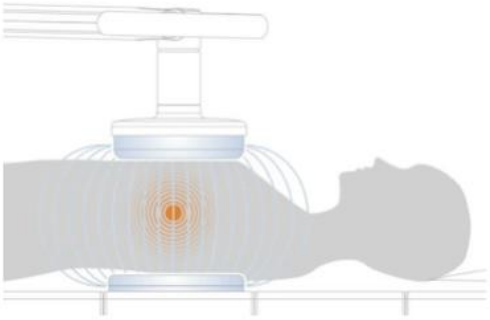
B. „ Local“ Hyperthermia“

Invasive:	Non Invasive:
RF, LITT, ECT, Intracavitary, peritoneal,…..	locale(surface) regional (deep region) = locoregional (=LHT)

Clinical Data

Feature	Celsius42 TCS	Oncotherm EHY - 2030	Oncotherm EHY - 2000 plus	Synchrotherm RF 1200	Andromedic HY - deep 600WM
Deep Regional Hyperthermia	√	X	X	√	√
Penetration Depth*	15.0 cm	n.a.	2 -5 cm	10.0 cm (500 W)	10.0 cm (500 W)
Clinical Studies Search Results Google Scholar	86	1	54	15	5

* Measurement by H. Sahinbas



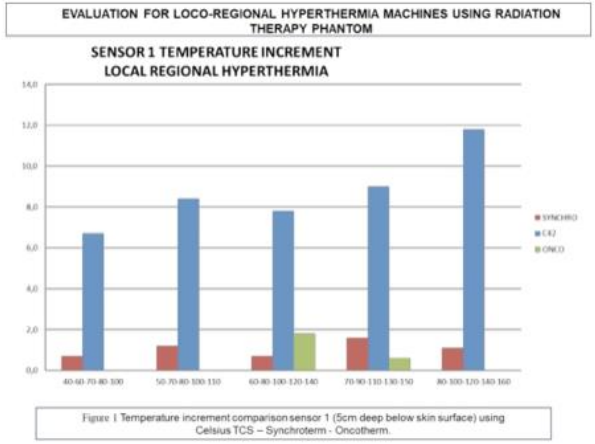
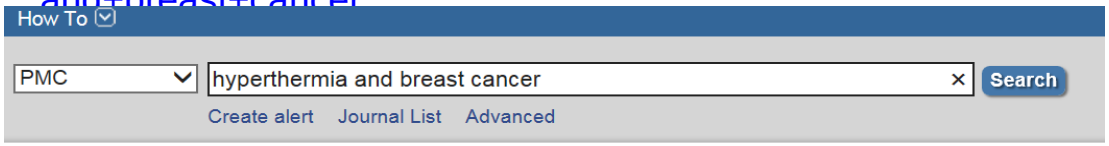


Figure 1 Temperature increment comparison sensor 1 (5cm deep below skin surface) using Celsius TCS – Synchroterm - Oncotherm.

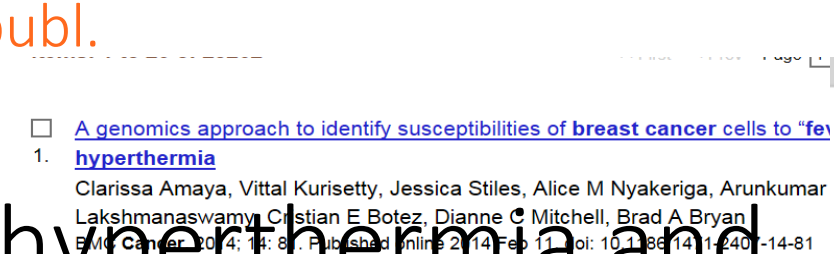
2018 © Celsius42 GmbH

hyperthermia and breast cancer:

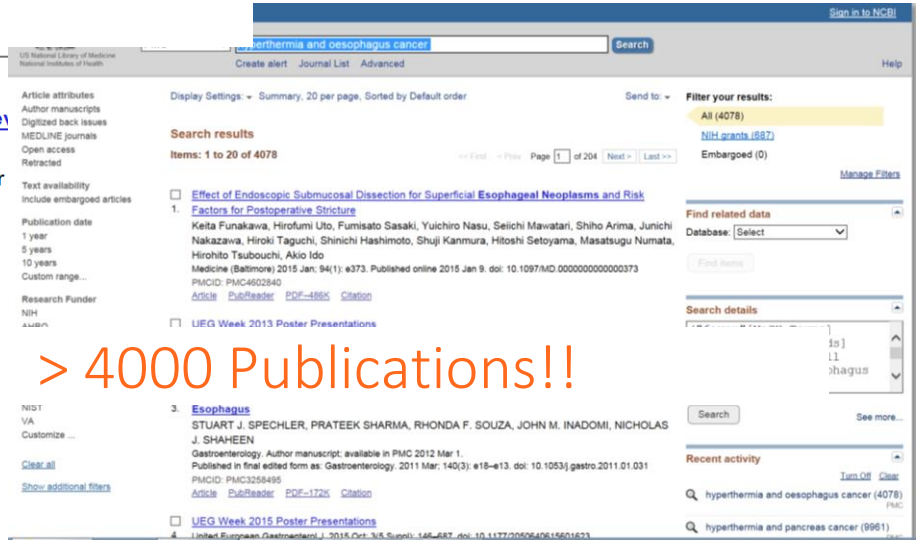
https://www.ncbi.nlm.nih.gov/pmc/?term=hyperthermia+and+breast+cancer



hyperthermia and breast cancer: > 23 tsd. publ.



hyperthermia and oesophagus cancer

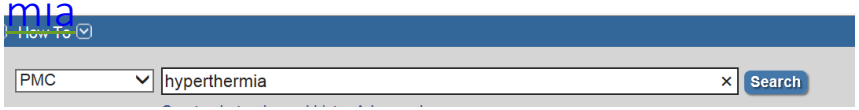


> 4000 Publications!!

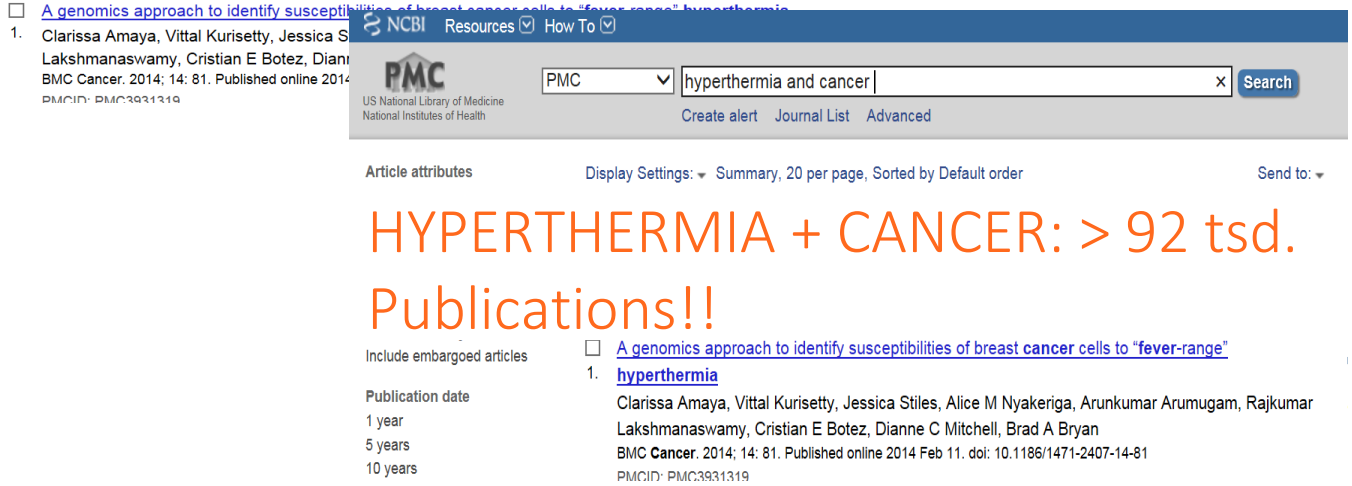
https://www.ncbi.nlm.nih.gov/pmc/?term=hyperthermia+and+oesophagus+cancer

PubMed 09/2018- HYPERTHERMIA + CANCER:

https://www.ncbi.nlm.nih.gov/pmc/?term=hyperthermia



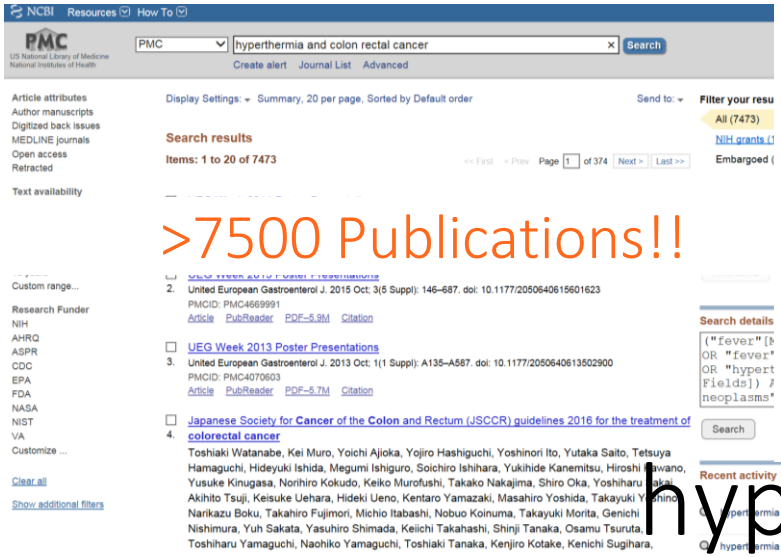
HYPERTHERMIA: 340 tsd. Publications!!

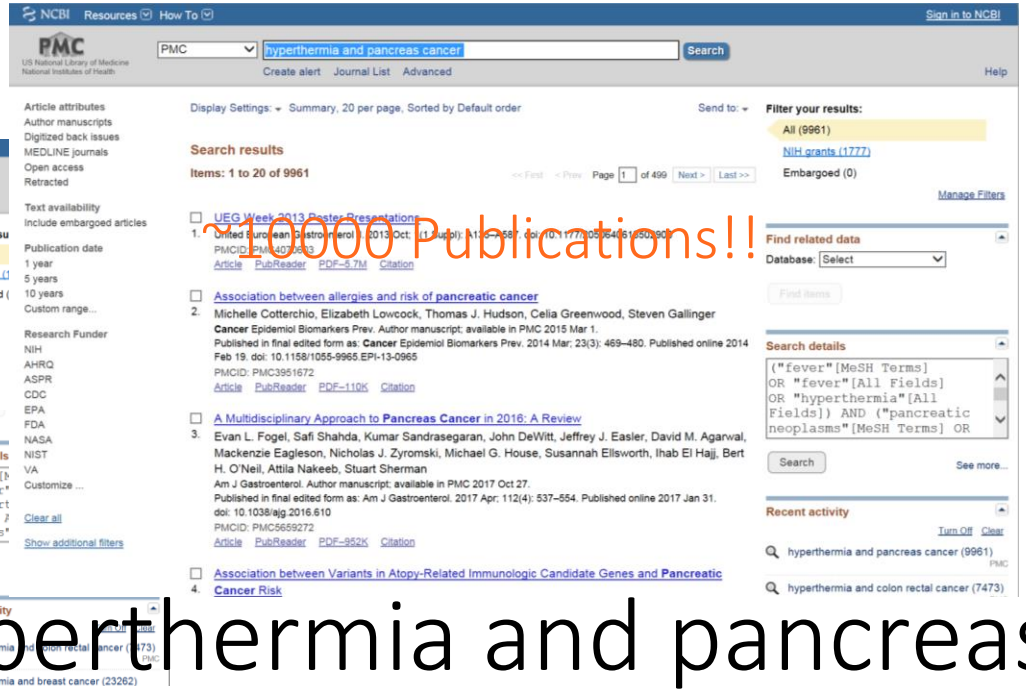


HYPERTHERMIA + CANCER: > 92 tsd. Publications!!

hyperthermia and colon rectal cancer

https://www.ncbi.nlm.nih.gov/pmc/?term=hyperthermia+and+colon+rectal+cancer





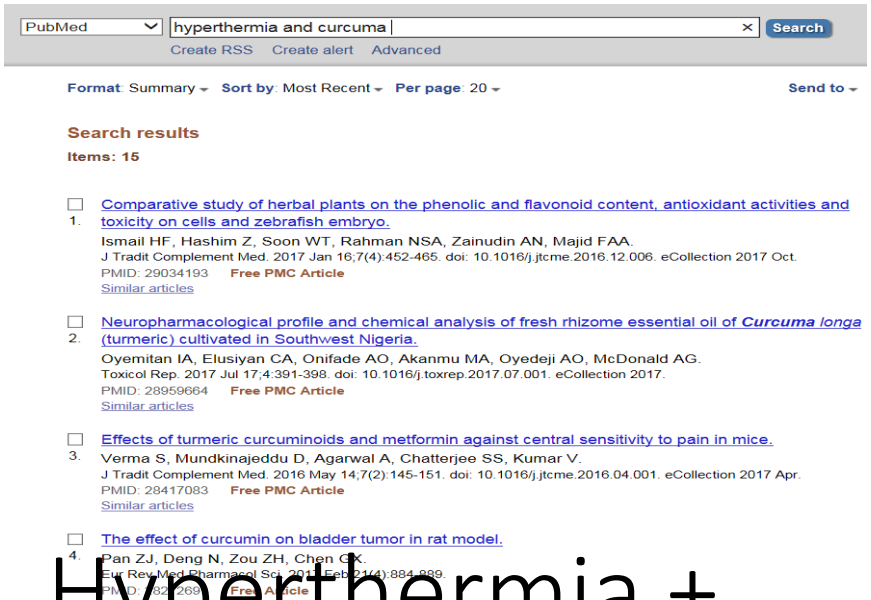
hyperthermia and pancreas cancer

https://www.ncbi.nlm.nih.gov/pmc/?term=hyperthermia+and+pancreas+cancer

Hyperthermia + chemo drugs

https://www.ncbi.nlm.nih.gov/pubmed/?





Hyperthermia + curcumin

https://www.ncbi.nlm.nih.gov/pubmed/?term

About the concept of hyperthermia:

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· One Word „Hyperthermia“ but three different therapy concepts (plus a variety of methods and objectives in each !)



Hyperthermia to boost **radiation** effects



Hyperthermia to boost **chemotherapy** effects



Hyperthermia to boost **immunological** effects

?



Hyperthermia as direct cyto-static cell death

Radiosensitizing Hyperthermie CELSIUS42
Effects in combination with radiation

CELSIUS 42

A. Increased Oxygenation in cells within region of interest

Gamma radiation create free oxygen radicals which in turn damage DNA of cells
Via hyperthermia ➒ better circulation ➒ increased supply with oxygenation

A systematic review of 4805 patients from 32 randomised trials provided level IA evidence that hypoxic cell sensitisation along with RT can achieve significantly improved rates of loco - regional tumour control, disease -specific survival, and overall survival in HNCs

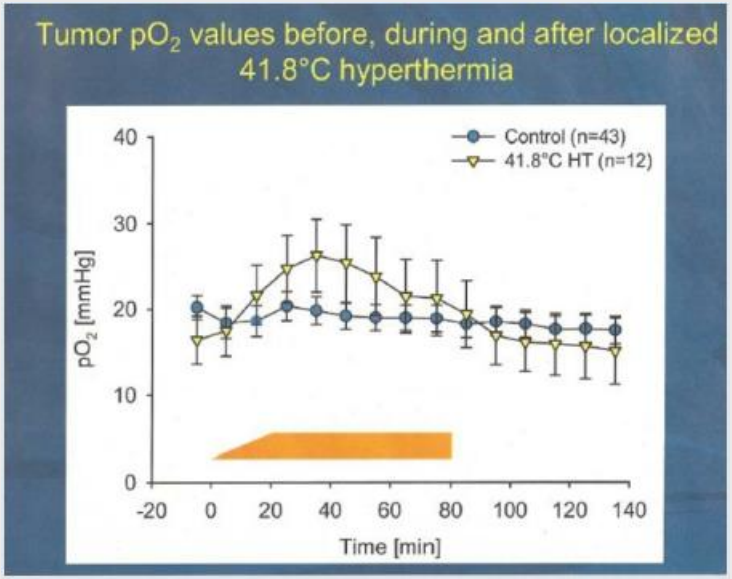
Overgaard J. Hypoxic modification of radiotherapy in squamous cell carcinoma of the head and neck – a systematic review and meta - analysis. Radiother Oncol 2011;100:22–32. quoted from Datta et al 2015

Radiosensitizing Hyperthermie CELSIUS42
Effects in combination with radiation

CELSIUS 42

A. Increased Oxygenation in cells within region of interest

Gamma radiation create free oxygen radicals which in turn damage DNA of cells
Via hyperthermia ❾ better circulation ❾ increased supply with oxygenation



Peter Vaupel, Univ Mainz 2008
presented at ISSOT 2008 Sapporo, Japan

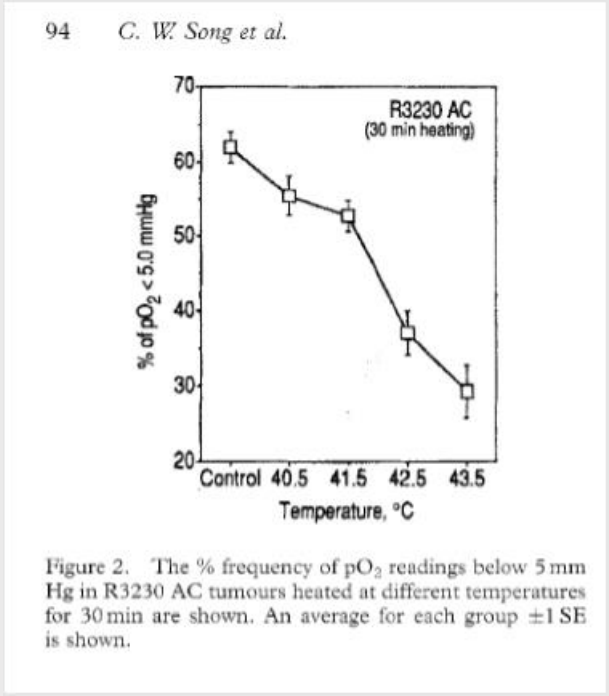

94 C. W. Song et al.

Figure 2. The % frequency of pO_2 readings below 5 mm Hg in R3230 AC tumours heated at different temperatures for 30 min are shown. An average for each group ±1 SE is shown.

Song et al Int.J.Hyperthermia March 2009,25 (2): 91 -95
originally 1995

❾ indicates:
to apply a mild

hyperthermia
before radiation

Radiosensitizing Hyperthermie CELSIUS+
Effects in combination with radiation

PET -CT scans on oxygenation proof an increase for the next 1 hour but moderate even for a time span of several days .
(Lüdemann et al 2009):

Conclusion: Lüdemann et al 2009

Conclusions: The increase in partition coefficient reflects an increased diffusion distance of radio-labeled water. Therefore water diffusion is increased due to hyperthermia. Analogous to water diffusion, the diffusion of inert gases is also facilitated, improving the oxygenation of hypoxic tumor cells. Our results suggest that tumor oxygenation can probably be enhanced by regional hyperthermia for a period of more than 1 h after heating, provided hyperthermia is applied for at least 60 min. The effect was observed to be reversible within one week.

L.Lüdemann, G. Sreenivasa, H.Amthauer, R.Michel
J.Gellermann, P.Wust, in: Int.J.HT June 2009 25 (4): 299 - 308
Use of $H_2{}^{15}O$ Pet for investigating perfusion changes
in pelvic tumors due to regional hyperthermia

Radiosensitizing Hyperthermie CELSIUS+
Effects in combination with radiation

B. Thermical stress after radiation inhebits DNA repair - mechanism ; „Fix the Damage“.

Among other aspects hyperthermia leads to an accumulation of proteins in the cell nucleus which bind itself to the nuclear matrix and thus inhebit the intra cellular repair of radiation damaged DNA sequences .

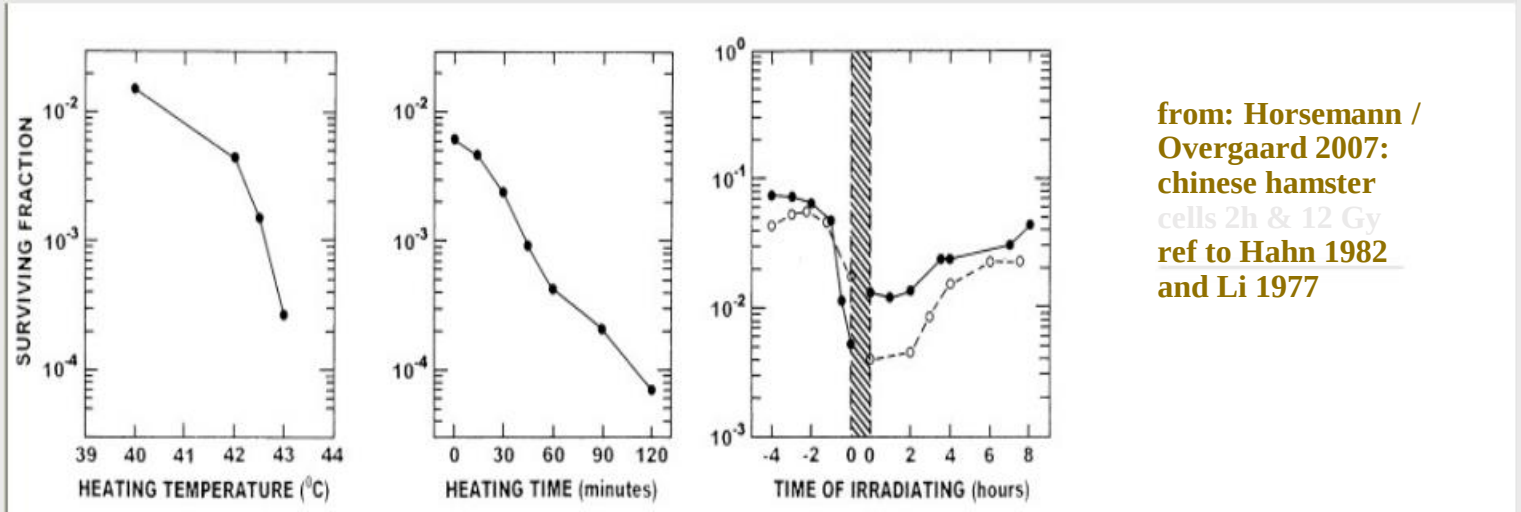
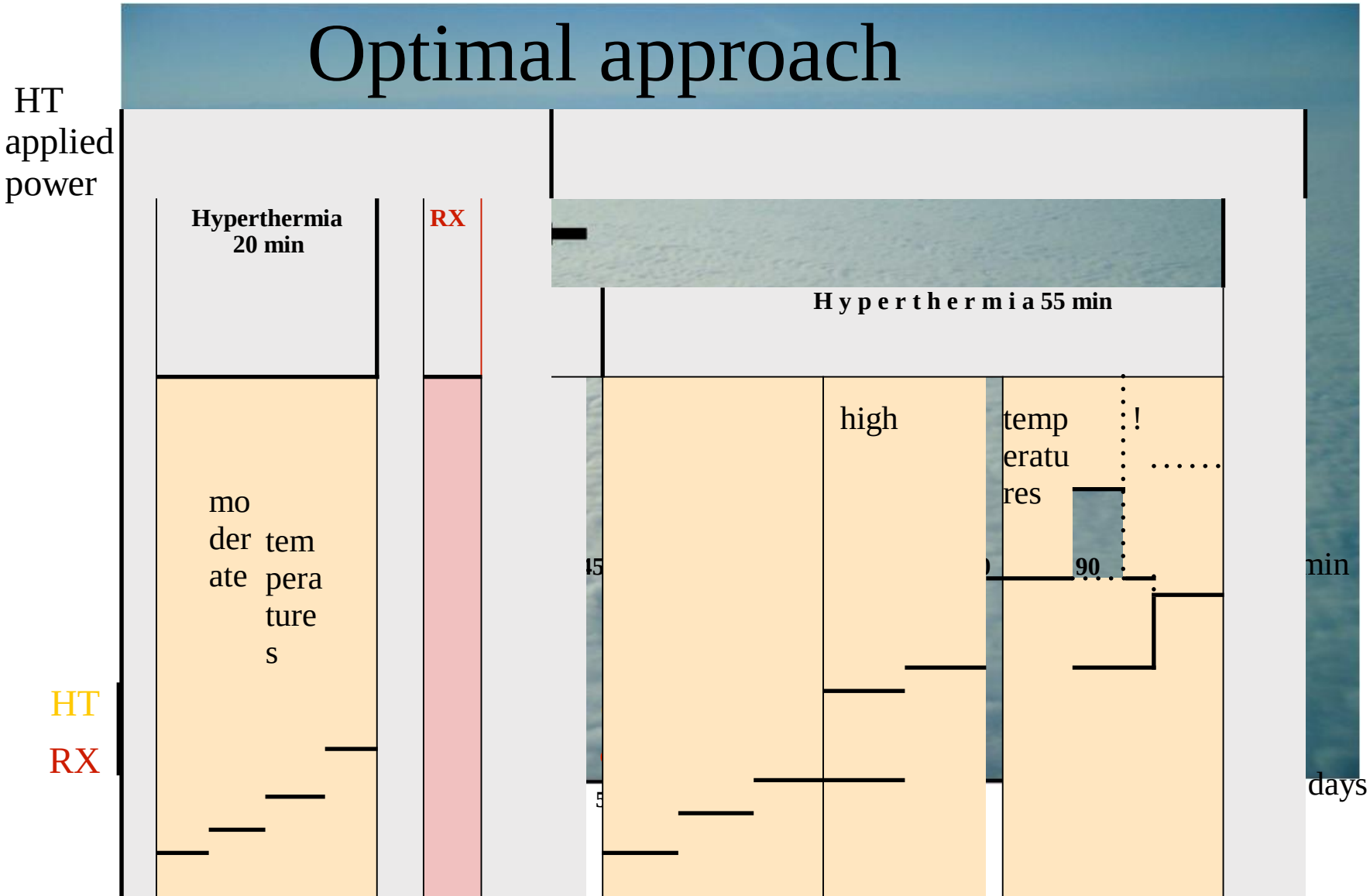


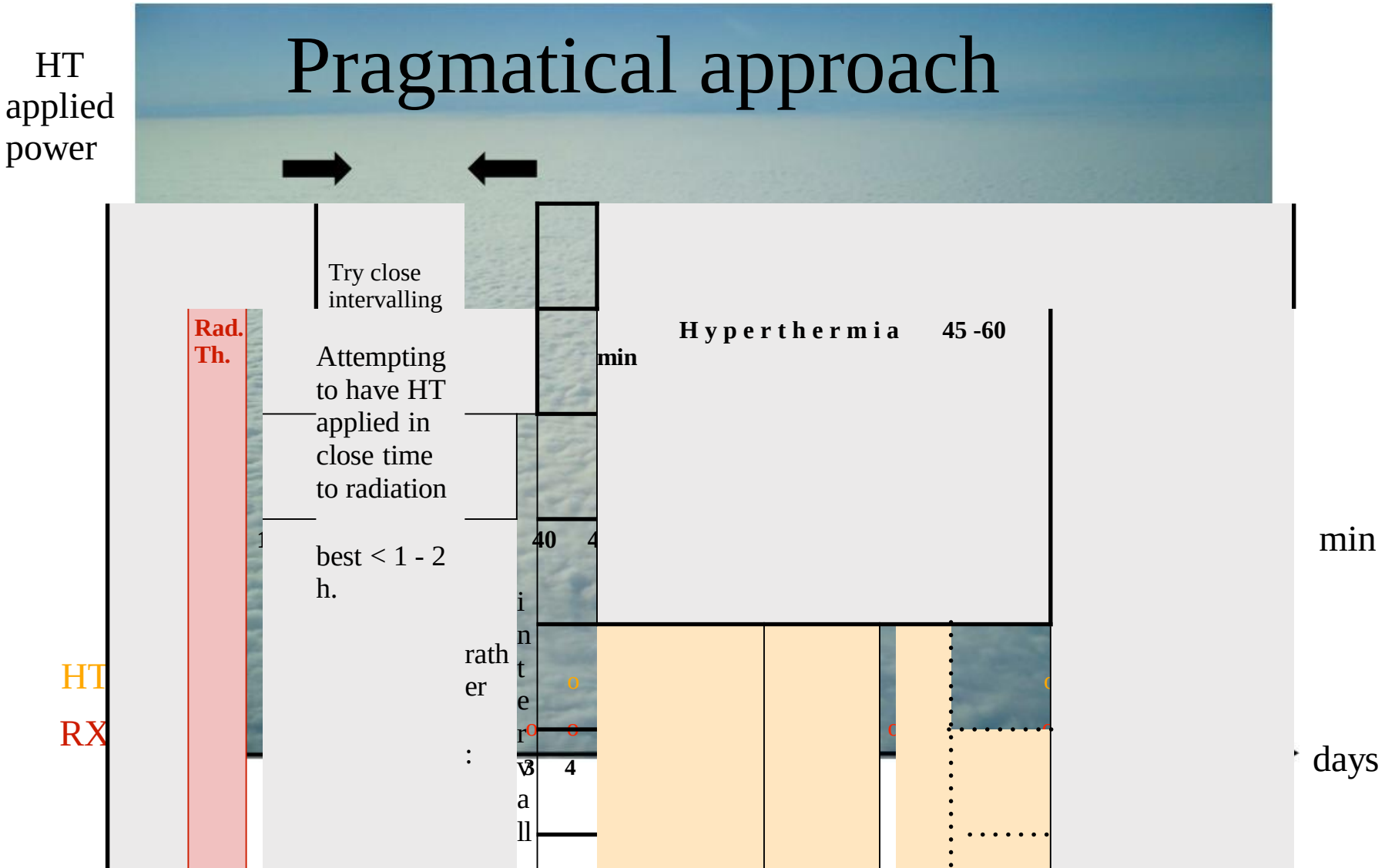
Fig. 1. Left panel: survival of Chinese hamster cells exposed to different heat temperatures for 2 h and irradiated with 12 Gy in the middle of the heating period. Middle panel: response of HA-1 cells to irradiation with 12 Gy and then immediately heated at 43°C for different times. Right panel: effect of heat (43°C; 60 min) and radiation (6 Gy) on the response of EMT-6 (○) or HA-1 (●) cells. The heating period is shown by the shaded area, with the irradiation given at different times before or after heating. Figures redrawn from [9] and [10].

from: Horsemann / Overgaard 2007: chinese hamster cells 2h & 12 Gy ref to Hahn 1982 and Li 1977

Radiosensitizing Hyperthermia CELSIUS TCS
Recommendations to schema and therapy protocol



Radiosensitizing Hyperthermia CELSIUS+ TCS
Recommendations to schema and therapy protocol



Hyperthermia & Radiation

Summary Rationale

* increase oxygenation
* inhebit DNA repair mechanism
* prolongates (RT sensitive) G2 cell cycle arrest
* positively interrelates with immune response

Hyperthermia – temperature
the case of Ellen Jones phase III trial

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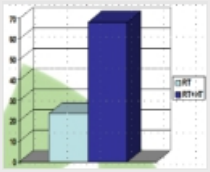
Breast

Jones et al. (J. of Clin.Oncology Vol.23.;13, 2005)

109 Patients with breast CA close to skinsurface

compr. response rate of 68,1 % radiation + HT
vs. 42,3 % radiation alone

most significant difference with patients previously radiated :
68,2 % in radiation+ HT
vs. 23,5 % radiation alone



In consequence to this trial:

The US NCCN has included combination treatment of RT and HT in their guidelines for breast cancer recurrals.

What made Ellen Jones start out? ❾ unsatisfying results in Vernon ´s * mamma trial with the critics that Vernon did not care enough about reaching a sufficient temperature.

❾ Thus she made sure in every case to truly reach the desired 10 CEM 43 ^{0}C

* Vernon et al. Int J Radiat.Oncol Biol Phys 35: 731- 744, 1996

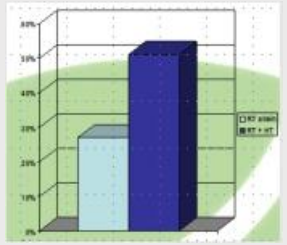
Hyperthermia
beneficial adjuvant treatment in oncology

Cervix

van der Zee/ Franckena et al (ESHO 2007, LANCET 2000)

rand. phase III trial **n>300** +12 years follow up 58 pat. (Rad.+HT) vs. 56 pat. (Rad.solo

* better lokal Control: 36 % (radiation alone)
  vs. 56 % (radiation + HT)



* Overall Survival 3 years 25 % (radiation alone)
  vs.>50% (radiation + HT)

* Ov. Survival >12 years: 20 % (radiation alone)
  vs. 37 % (radiation + HT) at p=0,02)

Franckena et al, June 2007, 24th Annual Meeting of ESHO, Prag, Abstracts S. 18) related to*:*
van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors : a prospective randomized multicentric trial . Lancet 2000; 335: S.1119 - 1125

@ Cervix phase II trial

CELSIUS 42

Tomsk Cancer Research Institute, Russia

· The study included 28 patients with cervical cancer Stage (FIGO): IIb – 10 , III – 17, IV – 1 (thereby recurrences: 2; HIV/HBV/HCV: 9)

· All patients received radical radiation therapy and venous cisplatin 40 mg /m2 (n -22) or gemzar / cisplatin (n -6) /weekly

· Local hyperthermia: multiplicity - 2 sessions per week; 8-10 sessions

· Median follow-up - 16 ± 2,1 months

Results (presented by Prof. **Startseva Zhanna at DGHT, Berlin2015)**

· decrease in pain and a reduction of bleeding from the genital tract no cases of profuses bleeding

· Early radiation reactions: 5 (18%) patients cystitis, 3 (11%) cases – radiation epithelium, 1 (3%) - enterocolitis

· 16 (57. 1 %) patients - complete response of the tumor,
11 (39 .3 %) partial regression
1 (3 . 6 %) stabilization of tumor

Hyperthermia in Head & Neck CA as beneficial adjuvant treatment in oncology

A **Nonresectable head /neck tumors Stage IV with metastasis in lymphnods**
randomized phase III trial (Valdagni und Amichelli , Italy)
Radiotherapy (RT) + regional Deep Location Hyperthermia (HT); n= 41 Patients

RESULTS: C **omplete Remission : 41 % in solo arm RT**
83 % in arm of combining RT + HT
5 - years Survival Rate: 0 % in solo arm RT
53 % in combining RT + HT

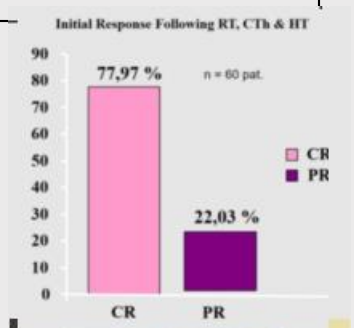
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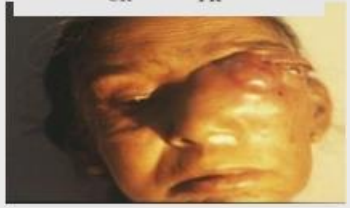
B **Non resectable Head & Neck Cancer** (Huilgol, Mumbai, India (2015))

60 patients: combining radiation therapy with hyperthermia (1x/week 45 – 90 Min.)
initial results: 46 patients CR complete remission ; 14 patients PR partial remission .
Overall Survival (OS) after 6 months: 84 %; after 24 months: 66 %.

Non resectable Head & Neck Cancer (Huilgol, Mumbai Indien; ESHO 2007)
23 patients; after common treatment with radiation (70 Gy) and chemo (either 60 mgs Paclitaxel or 50 mg Cisplatin/week) combining radiation & HT applied after radiation (30 -50 min). This three base treatment concept was well accepted by all patients. Initial Results: 10 patients CR; 13 patients PR.

Side Effects - thermal burns: Gr.0 51 pat; Gr.I 4 pat.; Gr.II 4 pat. und Gr. III 1 pat





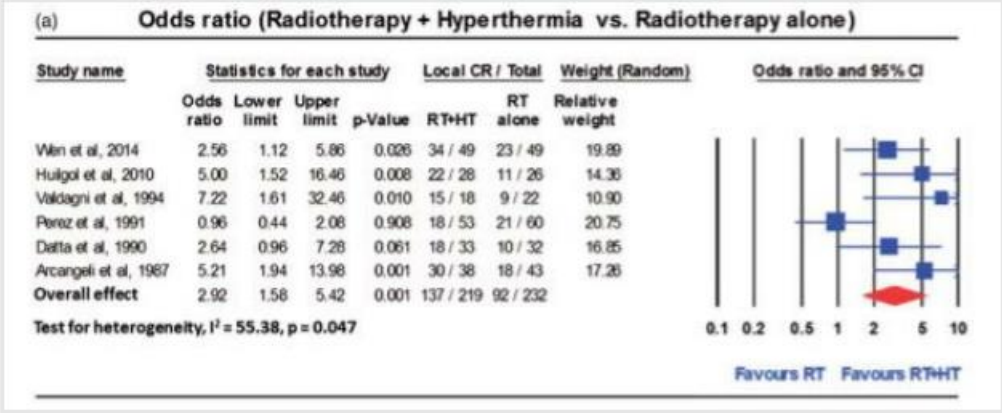


Head & Neck CA: A Systematic Review & Meta-analysis

Datta et al: Hyperthermia in H&N CA, Int J Hyperthermia. **2016**;32(1):31- 40

· 498 publications were reviewed => 6 trials => 5 randomized trials

· The overall CR with radiotherapy alone was 39.6% (92/232) and varied between 31.3% and 46.9% across the six trials. With thermoradiotherapy, the overall CR reported was 62.5% (137/219), (range 33.9– 83.3%). The odds ratio was 2.92 (95% CI: 1.58– 5.42, p¼ 0.001); the risk ratio was 1.61 (95% CI: 1.32 – 1.97, p50.0001) and the risk difference was 0.25 (95% CI: 0.12 – 0.39, p50.0001), all in favour of combined treatment with hyperthermia and radiotherapy over radiotherapy alone .
Acute and late grade III/IV toxicities were reported to be similar in both the groups.



Conclusion:

"Hyperthermia along with radiotherapy enhances the likelihood of CR in HNCs by around 25% compared to radiotherapy alone with no significant additional acute and late morbidities.

This level I evidence should justify the integration of hyperthermia into the multimodality therapy of HNCs"

Cochrane Review (Hyperthermia in rectal CA)

Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006269. doi: 10.1002/14651858.CD006269.pub2.

Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer . De Haas - Kock DF, Buijsen J , Pijls - Johannesma M , Lutgens L , Lammering G , van Mastrigt GA, De Ruysscher DK , Lambin P, van der Zee J .

Six RCTs published between 1990 and 2007 were identified. A total number of 520 patients was treated, 258 in the radiotherapy only arm (RT) and 262 in the radiotherapy- hyperthermia arm (RHT). Four studies (424 patients) reported overall survival (OS) rates. After 2 years, OS was significantly better in the RHT group (HR 2.06; 95% CI 1.33 - 3.17; p=.001), but this difference disappeared after a longer period (3, 4 and 5 year OS). All but one studies reported CR rates. A significant higher CR rate was observed in the RHT group (RR 2.81; 95% CI 1.22 - 6.45; p=.01). Only 2 studies reported on acute toxicity. In these 2 studies no significant differences were observed between the RT and the RHT group. Late toxicity data were not reported.

HCC and liver metastasis

Hyperthermia as adjuvant additional therapy option

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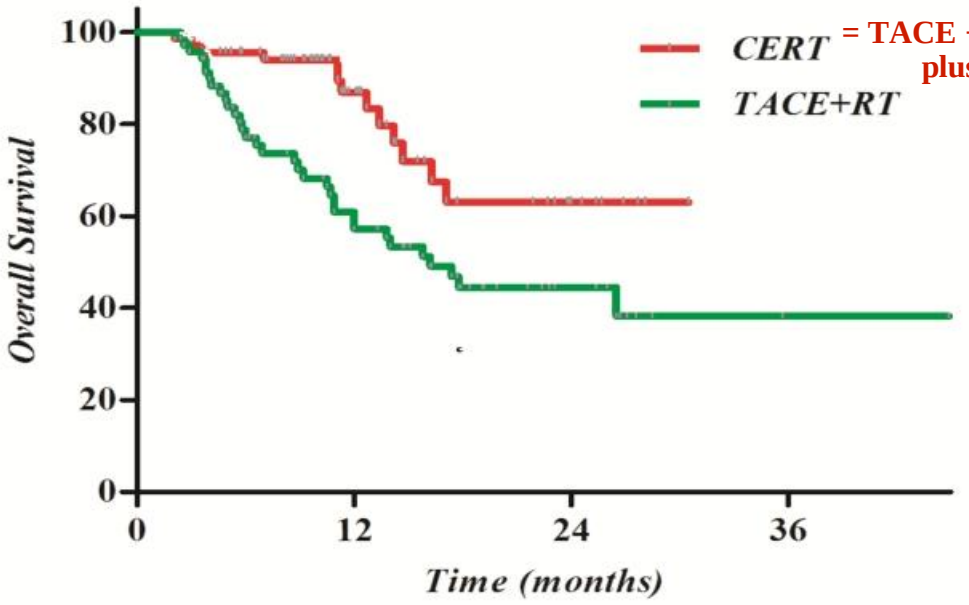
www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Combination treatment with transarterial chemoembolization, radiotherapy, and hyperthermia (CERT) for hepatocellular carcinoma with portal vein tumor thrombosis: Final results of a prospective phase II trial

Jeong Il Yu[1], Hee Chul Park[1,6], Sang Hoon Jung[1], Changhoon Choi[1], Sung Wook Shin[2], Sung Ki Cho[2], Dong Hyun Sinn[3], Yong-Han Paik[3], Geum-Youn Gwak[3], Moon Seok Choi[3], Joon Hyeok Lee[3], Kwang Cheol Koh[3], Byung Chul Yoo[4], Hüseyin Sahinbas[5], Seung Woon Paik[3]

[1]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
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arch, Partner of the Marien Hospital Herne, Hospital of the Ruhr-University Bochum,
nagement and Research, SAIHST, Sungkyunkwan University, Seoul, Korea
email: hee.ro.park@samsung.com

a, radiotherapy, hyperthermia, response, complication
Accepted: March 13, 2017 *Published:* April 13, 2017



= TACE + RT plus HT

Historical OS: TACE+TR with PVTT *

treatment - naïve patients

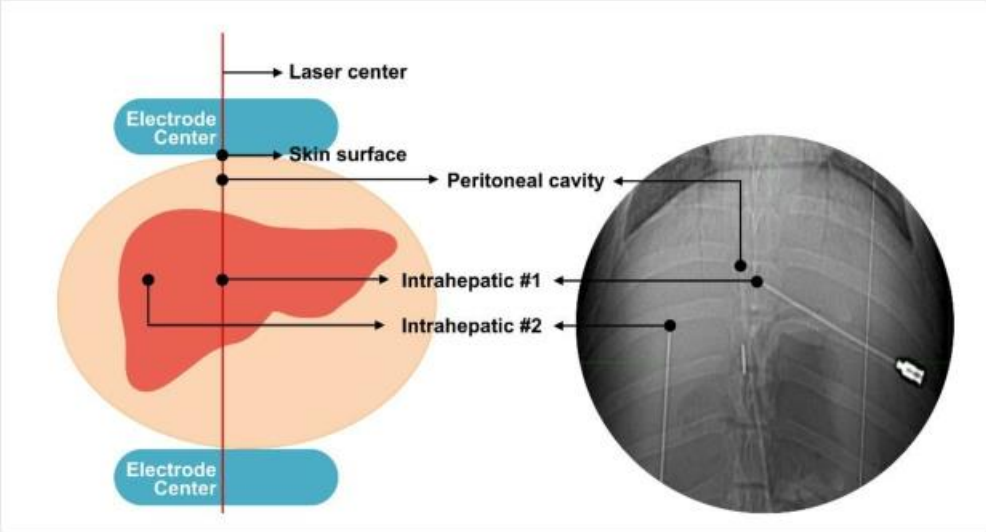
* TACE and RT for treatment - naïve patients with locally advanced HCC,

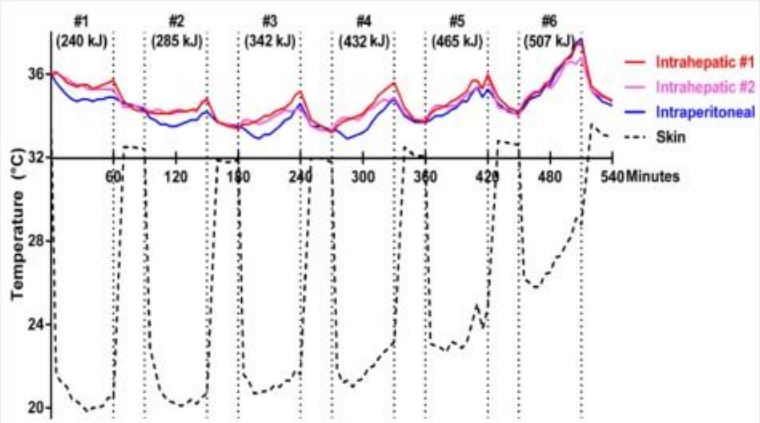
Sang Won Kim, et al., **Radiat Oncol J 2014**;32(1):14- 22, 03/2008 and 12/2010, N 204 patients
MedicinSamsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

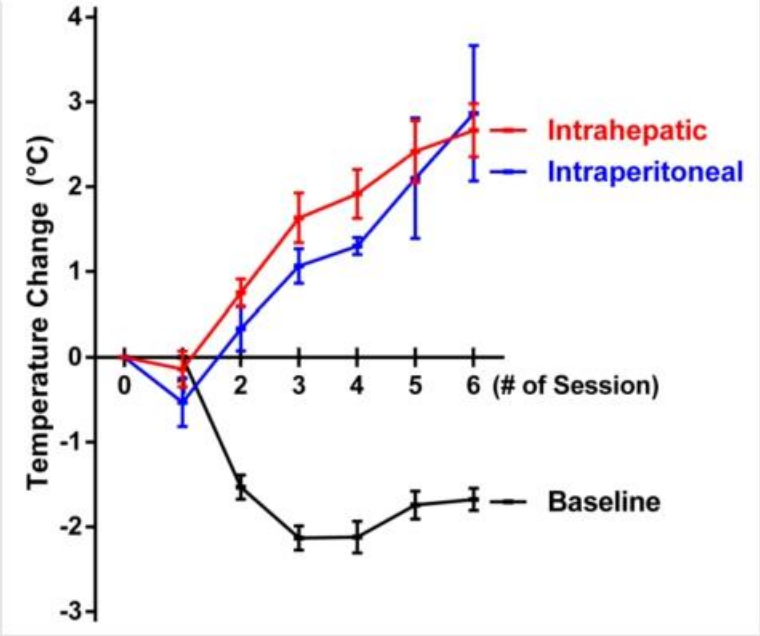
HCC and liver metastasis

animal (pigs) thermometry in liver

CELSIUS







Hyperthermia Schedule

- Provided by manufacturer (C42)
- Same with clinical study
- Pigs (#3)
- Under deep anesthesia
- invasive insertion of optical thermostats

Noh et al. Radiat Oncol J 2014;32(4):256 - 61

HCC and liver metastasis

CELSIUS

Case: hepatic metastases of colon CA

After therapy with capecitabin (XELODA ®) solo (July)



During therapy with capecitabin (XELODA ®) now plus HT (Nov)



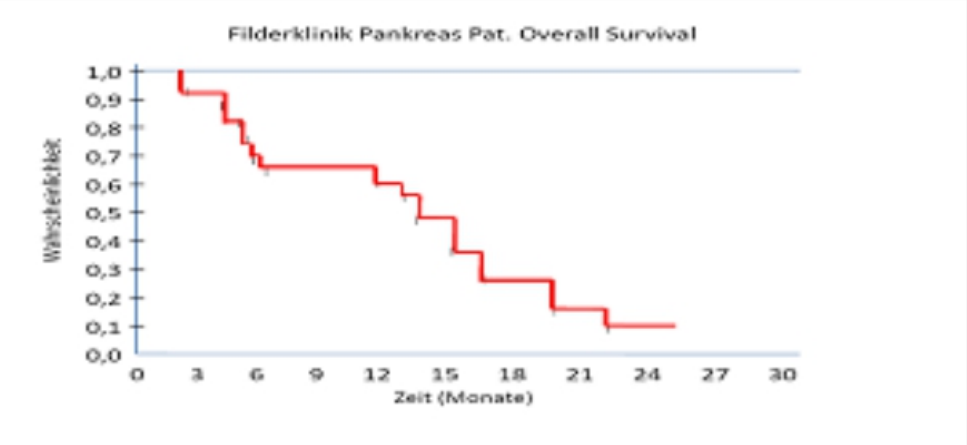
Non -resectable **pancreatic tumors**: Gemcitabine plus Hyperthermia

CELSIUS

Filderklinik, Stuttgart, Germany
Hämato- Onkologische Klinik
2014 Ä D Dr. Mueller - Huebenthal

Study included 25 patients of non - resectable pancreatic cancer with a median OS of 12,2 months comparing to about 6,7 months acc. to various randomized phase III trials with Gemcatibine monotherapy since 2001. 3 patients showed complete response, 7 patients partial response, four patients still alive. Thus cancer control (CR+PR+SD) was 65 % and one year survival 51% (versus expected 25%).

The treatment included a standard chemotherapy based on Gemcitabine combined with a loco regional session of hyperthermia of 1 hour duration twice a week. Negative side effects due to adding hyperthermia have not been observed in this clientel. Even a rise in quality of life in many of these patients have been observed as expressed Dr. Mueller - Huebenthal in presenting the data.



-non-resectable cases -

Mean Overall Survival: 12,2 months !
vs.
mOS Gemca solo ≈ 6,2 months

Pancreatic tumors

CELSIUS 42

3 initial trials presented at ICHO 2008 from Verona, Italy, München Germany & Kyoto – Jap.)

Takagi et al, Kyoto: for Gemcitabine **& HT** versus for Gemcitabine alone

57,1% Tumorcontr.(CR+PR+SD) ,, **14,3 %**

49 % 1 year OS ,, **30 %** (p=0,024)

Maluto et al , Verona: for Chemo /Radiation **& HT** versus for solo Chemo /Radiation

68 % 1 year OS ,, **47 %**

no additional side effects observed than in control group

Tschoep et al, München: for Gemcitabine/CIS & HT as second line therapy

median progression free survival from start 2nd line therapy:
4,2 months (CI: 2.1 -7.7); median OS: **16,9 months** (CI: 11,8 -22)

All presented at *ICHO conference , 10th International Congress on Hyperthermic Oncology, München April 2008*

Pancreatic tumors

INTERNATIONAL JOURNAL OF HYPERTHERMIA, 2017
https://doi.org/10.1080/02656736.2017.1401126

IJHT 2017

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The clinical benefit of hyperthermia in pancreatic cancer: a systematic review

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REVIEW: 14 trials with **395 patients** of locally advanced or metastatic pancreatic cancer of which 248 pat. were treated with hyperthermia.

Quality of trials are low, but six studies included a control group:

Median OS: ➽ **5,6 months vs. 11,7 months** in group with hyperthermia
Overall Response Rate ➽ **35,3 % versus 43,9 %** in group with hyperthermia

Brain tumors

A. Sahinbas/ Hager: 2001 -2008: 179 patients (ASCO 2008)

OUR RESULTS

Hyperthermia may increase overall median survival time (MST)

MST of patients with WHO grade III and IV gliomas (Kaplan-Meier-Estimation)		
MST from	Grade III; N = 53 pts months±se [95%CI]	Grade IV; N = 126 pts months±se [95%CI]
1st Diagnosis of Disease	37.0±3.7 [29.8;44.2]	19.0±1.6 [15.9;22.1]
1st RF-Hyperthermia	10.0±1.9 [6.3;13.7]	7.0±0.8 [5.4;8.6]
Censored N (%)	14 (26.4%)	25 (19.8%)



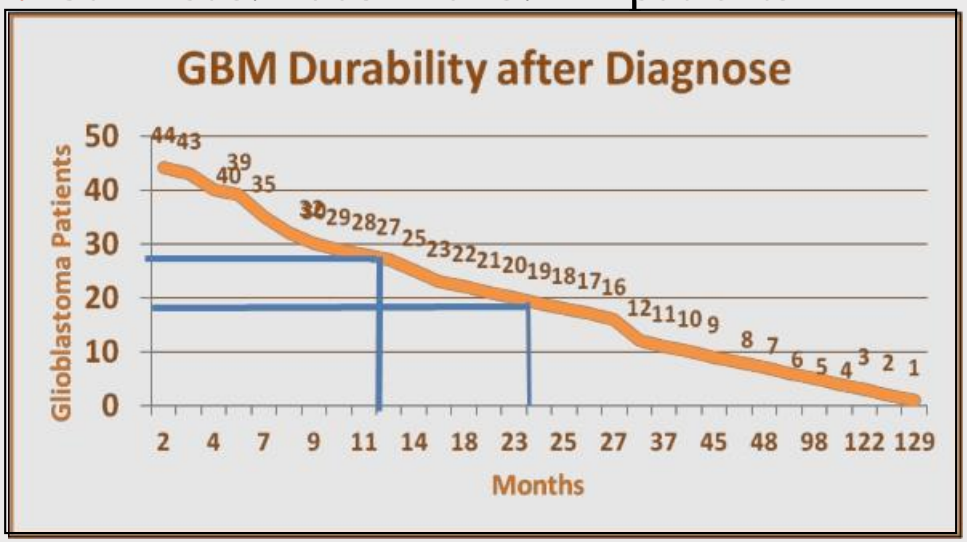
5 y. MST from 1° diagnoses (ASCO 2008 Hager, Sahinbas)

From newly diagnosed	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
AA WHO°III; N=53	96	72	53	35	30
GM WHO°IV; N=126	82	41	23	11	11

Kaplan-Meier-Estimation

Even though in this patient collective less than abt 40% received standard triple treatment of surgery, chemo and radiation,
outcome including HT is still as to best practic

B. Sahinbas: 2009 -2018: 44 patients



median survival time GBM (OS) = 19 Mon
27 Pts. from 44 alive after 12 Months ❾ ~61%;
19 pts. from 44 alive after 24 Months ❾ ~43 %

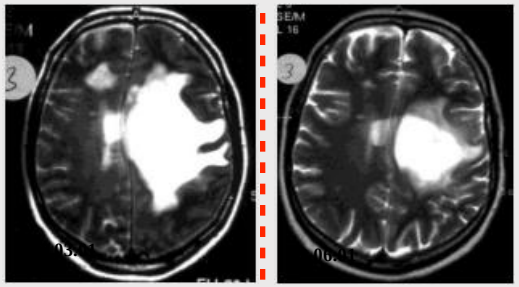
CASE: GBM (WHO stage IV)

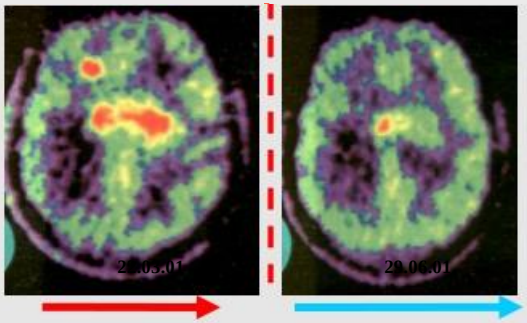
Patient : female, 30 years

Diagnosis: 1997 Grad I re. frontal + central , 2/00 ED Metastasis and.Recitives: Bifrontal and central, TNM - 2/00 Anaplastic Astrocytoma WHO III/IV Complete remission 2001

Radio-therapy : Seed - Implantation 3/00- 2/01 + 25 Gy,+ 25 Gy external Radiation

Other Therapies: 03.04.01- 05.05.01 Hyperthermia - Monotherapy, from 05.05.01 hyperthermia + Systemic Chemotherapy Temodal during 21 days 100 mg/Kg KG 21 days/ 1week

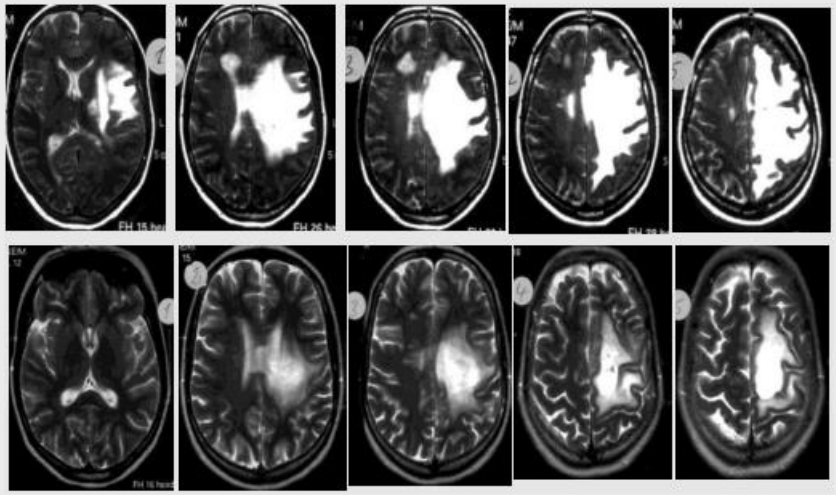




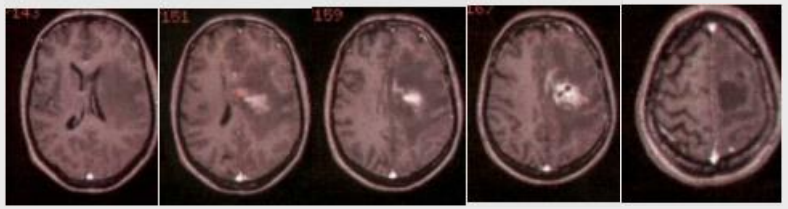
After radiation, before Hyperthermia

Hyperthermia +Temodal

22.03.01 before hyperthermia



21.08.01 after hyperthermia + Temodal



Control 29.10.01 after Hyperthermia+Temodal

Positioning of electrodes – Brain tumor







Quality assurance - difference of RF-HT-Systems

GUIDELINES:

international (ESHO) and German Hyperthermia society (IAH) under German Cancer society

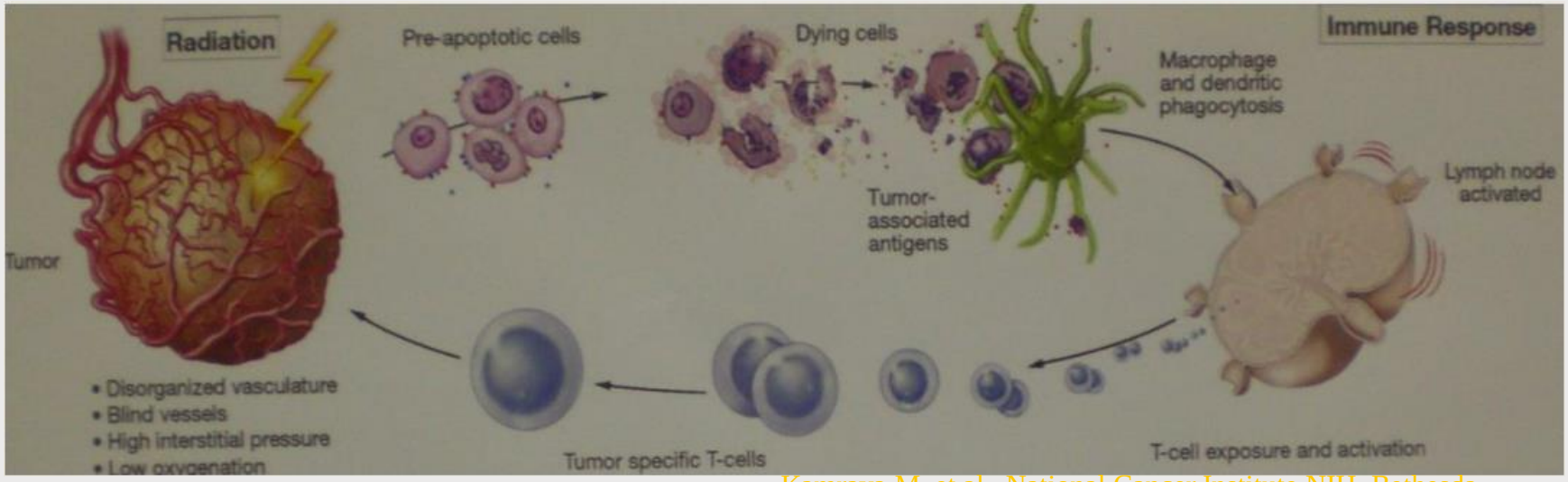
Qualitycontrol and Efficienzycontrol of locoregional Hyperthermia-Systems:

The Referenz SAR (Specific Absorbation Rate):

0,2 °C in 1 Min , or 1 °C in 5 Minuts and 10-12 °C in 60 Minutes

(without Perfusion) Publ. in „International Journal of Hyperthermia; Wust et al.

I rational multimodal treatment



Kamrava M. et al , National Cancer Institute NIH, Bethesda

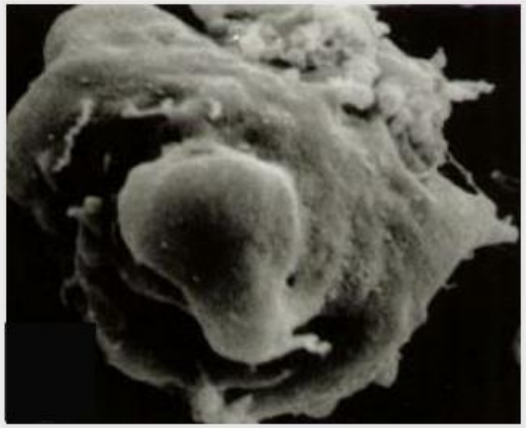
· Antigen Release from dying tumor cells as induced by radiation can activate immune response.

· These dying cells are taken up by the antigen presenting cells (APCs). These APCs then travel to nearby lymph nodes to present antigen to T cells; these activated tumor specific T cells are a most effective indigenous immune response to achieve tumor killing.

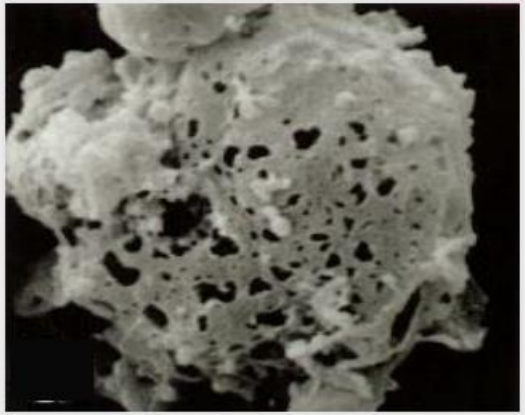
I rational multimodal treatment

CELSIUS 42

Apoptotic cell



Nectrotic cell



Pictures provided by
Marco Vitale et al.

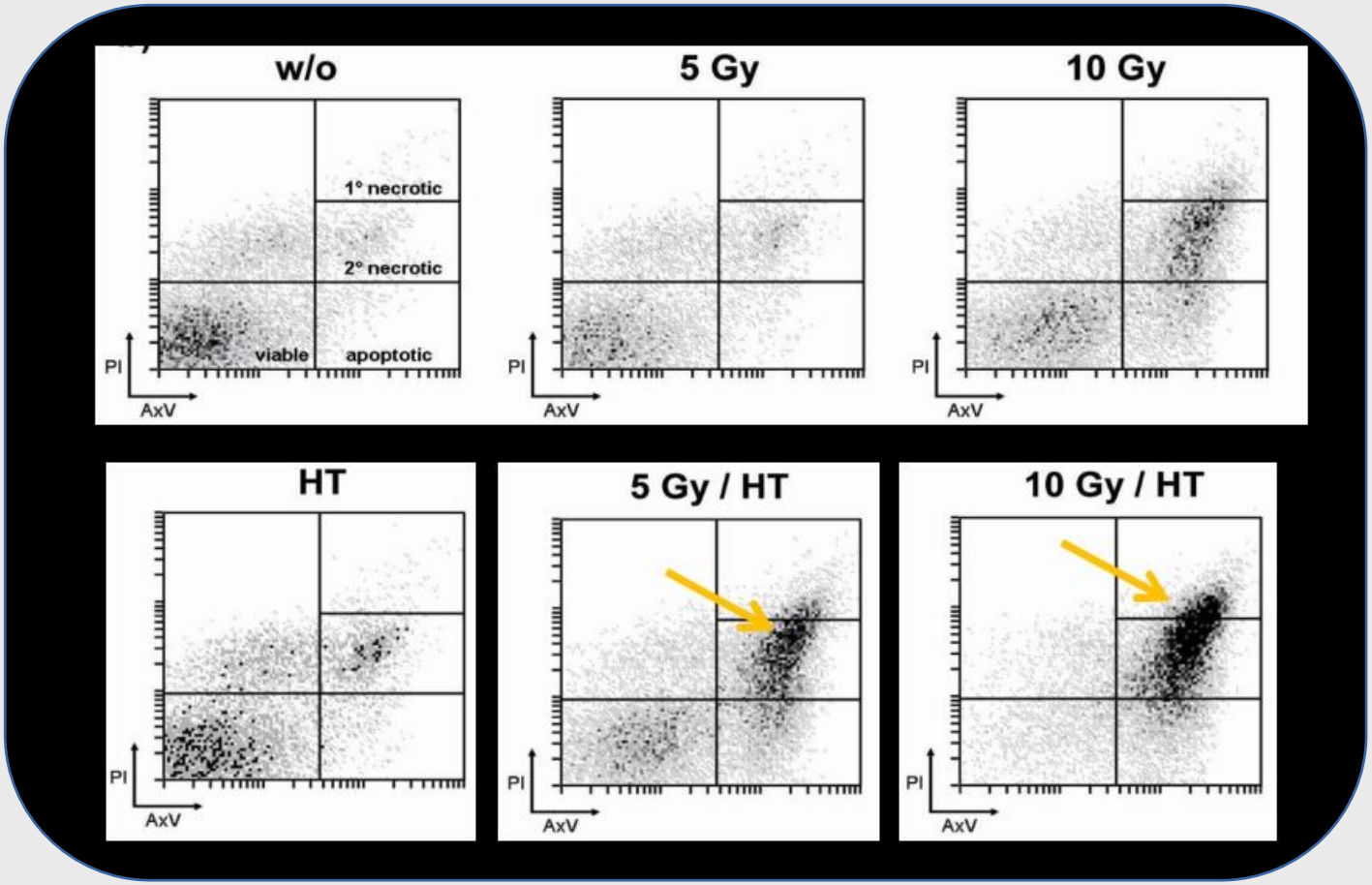
Reminder

! To trigger the adaptive immune response it requires nectrotic cells not apoptotic cell death !

I rational multimodal treatment

CELSIUS 42

Schildkopf et al., Biochem Biophys Res Commun, 2010

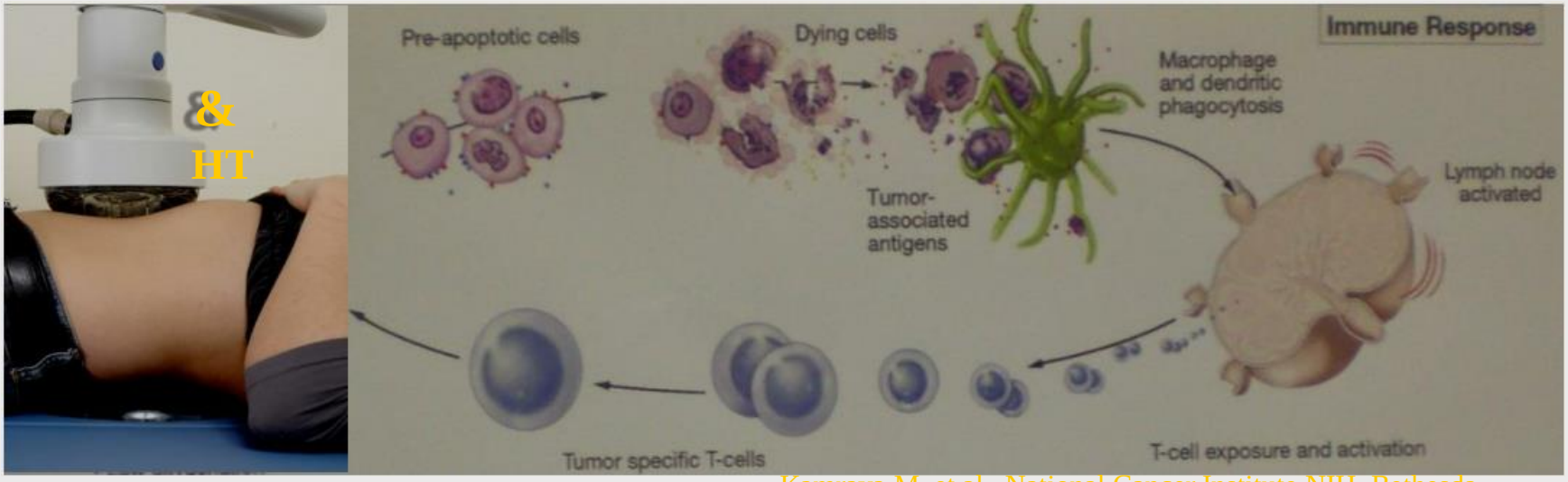


HCT15 colorectal tumor cells; 72 hours after treatment;
HT: 41.5 ° C for 1h; time interval between treatments: 4 hours

Fazit:

It ´s the combination of HT & RT that induces most nectrotic cells

II rational HT co-therapy



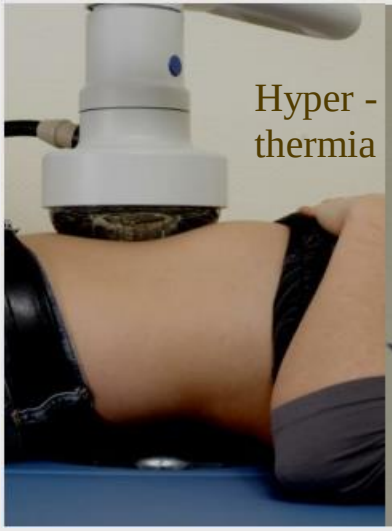
Kamrava M. et al , National Cancer Institute NIH, Bethesda

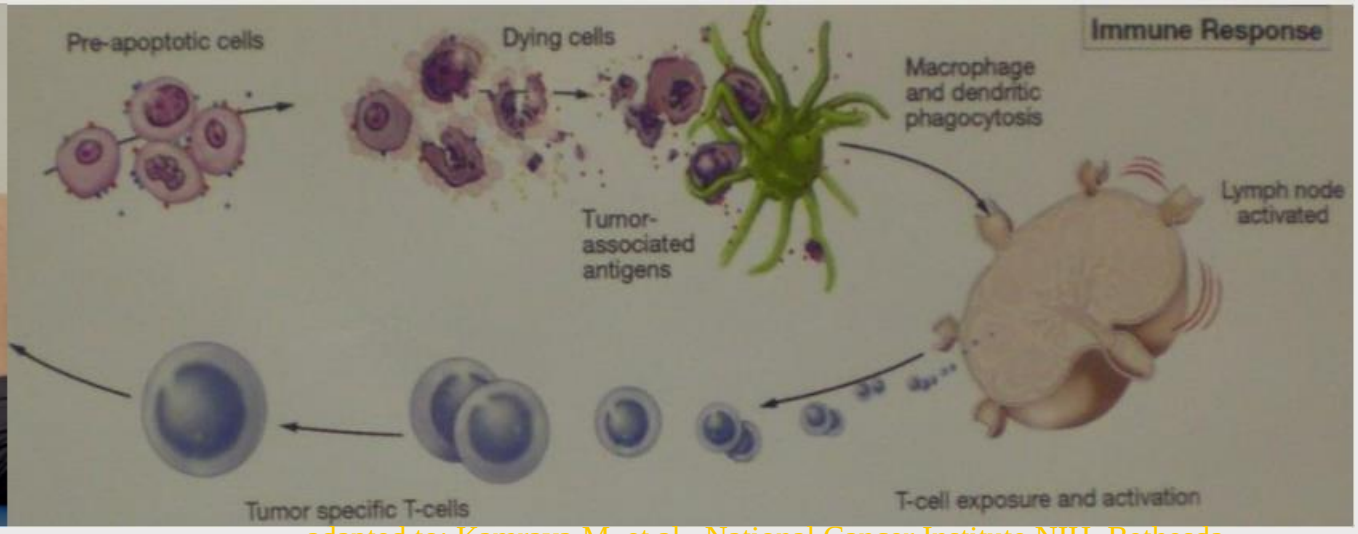
· Hyperthermia facilitates & enhances this process:
- ❾ decrease interstitial pressure
- ❾ increase tumor perfusion
- ❾ facilitate lymphotic trafficing (APCells & spec. T-cells)
- ❾ increase oxygen levels (before hypoxic tumor)

· **Thus: lymphatic traffiking ⬆ ❾ treatment more effective**

III rational HT co-therapy

CELSIUS



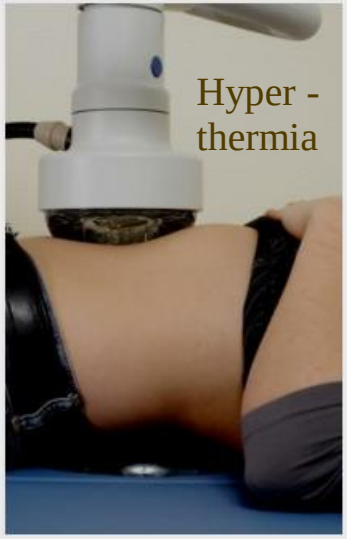


adapted to: Kamrava M. et al , National Cancer Institute NIH, Bethesda

Hyperthermia can induce antitumor immunity in very early apoptotic cells by exposing eat - me signals like calreticulin for dentritic cells.

Obeid M.et al ,Calreticulin exposure dictates the immuno - genicity of cancer cell death. Nat.med.2007; 13 (1):
Gaipl U.et al , Hyperthermia in Oncology, hsg. von O.Ott, R. Issels, R. Wessalowski, 2010) :54;

IV rational HT co-therapy



plus general effects:

NK cells operate more efficient in raised temperatuer levels (Multhoff Munich)

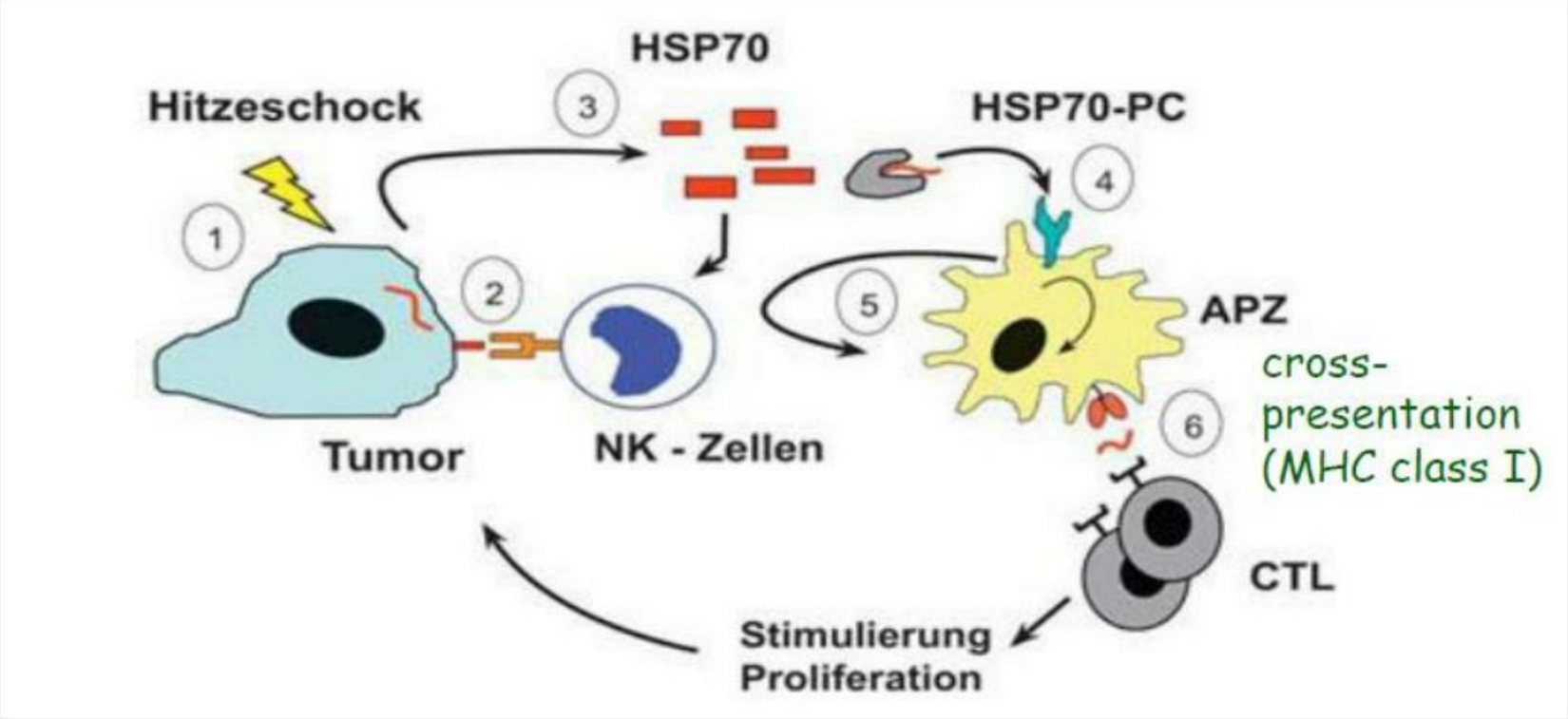
Helps suppress inflammatory processes (which in turn supress immune system)

V rational HT co- therapy

CELSIUS 42

adapted from G.Multhoff et al & U.Gaipl

Heat Shock Proteins: HSPs



HSPs: **inside the cell:: thermo tolerance**

outside the cell : immune activating danger signal

V rational HT co -therapy

CELSIUS 42

Findings: Schildkopf and Frey et al, Radiother Oncol , 2011

- **Hyperthernia induces release of HSP70 (no surprise)**
- **Radiation however induces higher surface expression of HSP70 !**

Summary: 1+1 = 3

Hyperthermia & Immuntherapy

Summary Rationale

* facilitates lymphathic trafficing
* NK cells more effective in raised temp . levels
* evokes HSP70 / HSP90 as eat - me- signals
* positively interrelates with immune response

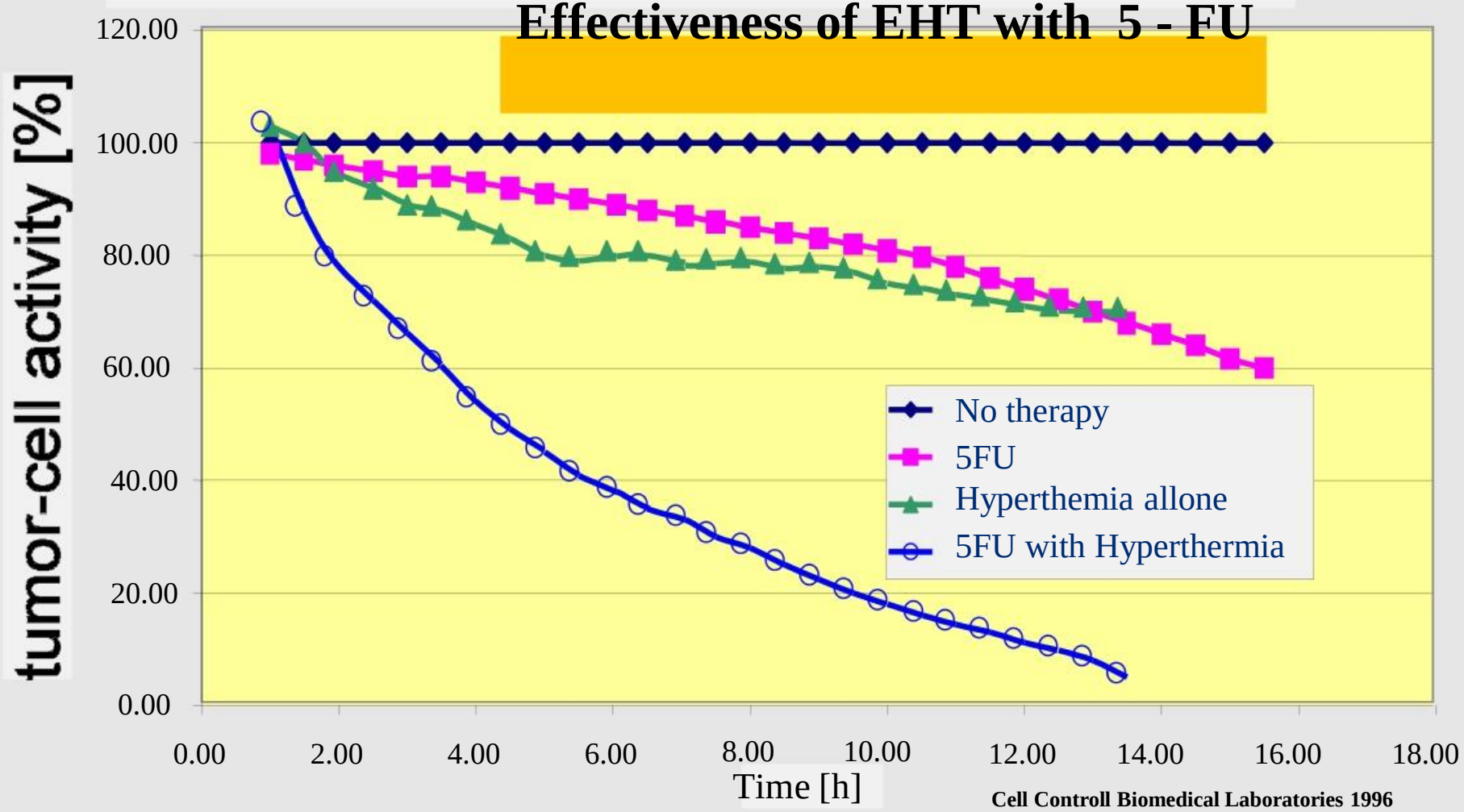


The Rationale of Hyperthermia

- Supporting Chemotherapy

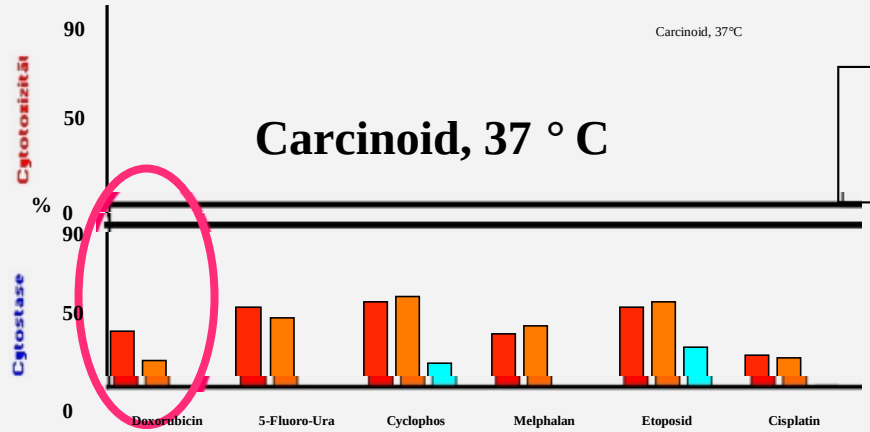
Effect in combination with chemotherapy

Sensibilisisation, Potentiation of Chemotherapeutics
Effectiveness of EHT with 5 - FU



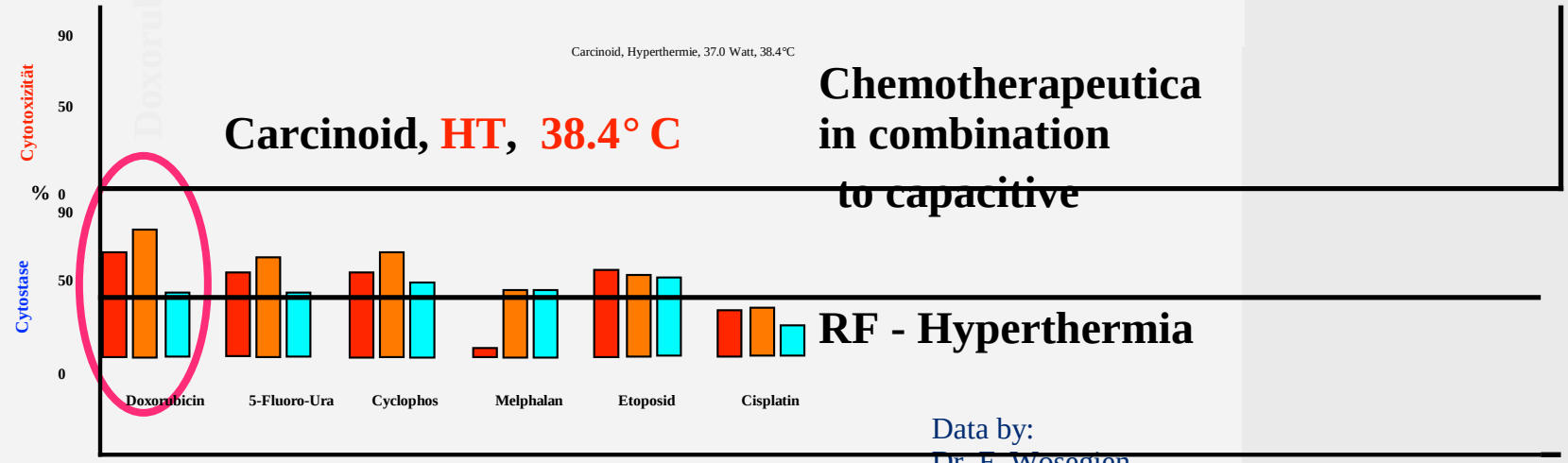
Cell Controll Biomedical Laboratories 1996

Effects in combination with chemotherapy



Carcinoid, 37 ° C

Chemotherapeutica solo



Carcinoid, HT, 38.4° C

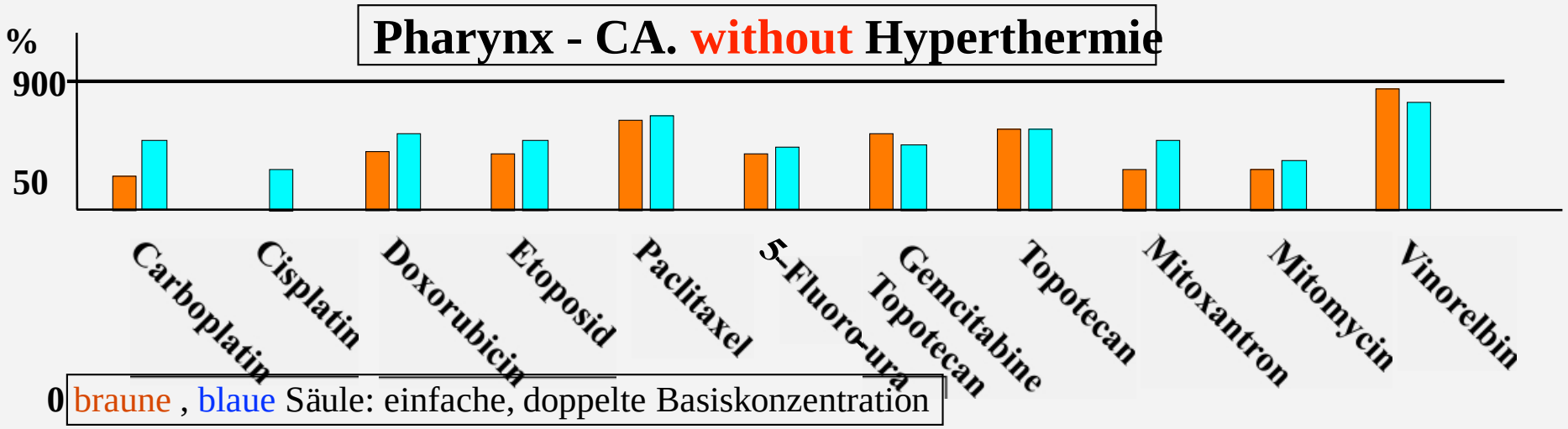
Chemotherapeutica in combination to capacitive

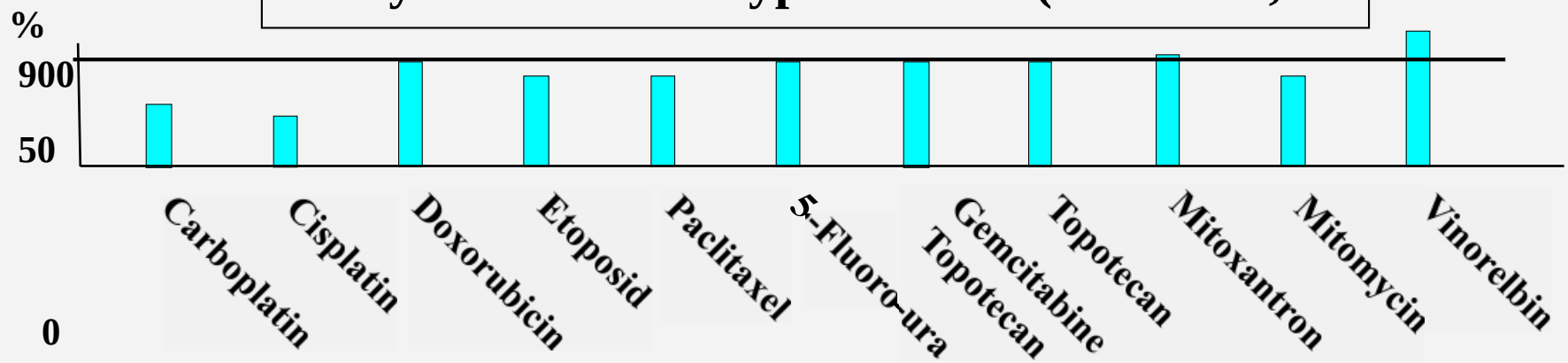
RF - Hyperthermia

Data by:
Dr. F. Wosegien
Limbach Laboratories

rote, braune, blaue Säule: halbe, einfache, doppelte Basiskonzentration. Die Basiskonzentration e. Substanz richtet sich nach dem Plasmaspitzenwert bei systemischer Gabe in üblicher Dosierung.

Effects in combination with chemotherapy

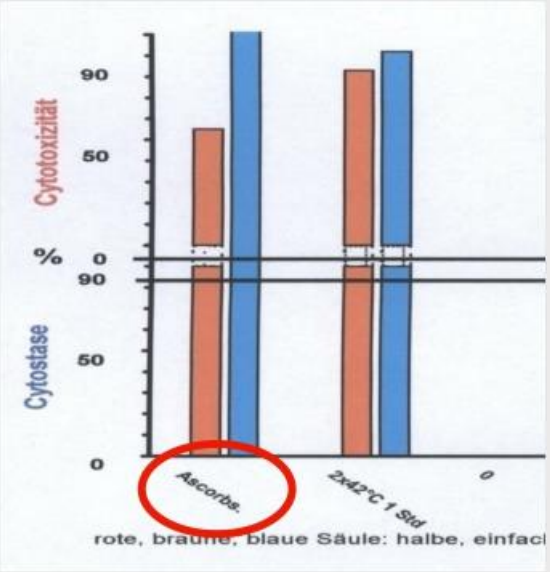




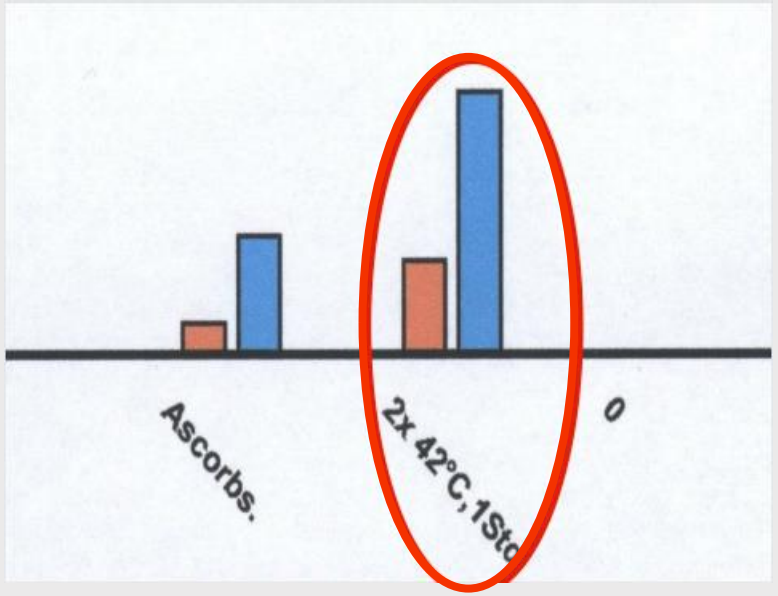
Effects in combination with chemotherapy

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13.56 MHz - RF- HT 120, 30 Minuten, 42.5 ° C



Vit C vor/nach Hypr. bei Tuben Ca.



Vit C vor/nach Hypr. bei Pankreas Ca .

Vit. C without HT and after 30 min of Hyperthermia

Why is Hyperthermia beneficial to Chemotherapy ?

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Moderate temperatures in ROI :

a) ❾ enhance metabolismus in cell
   ❾ thus uptake of cytostatica ⬆ (pharmakokinetic acceleration)

b) blood flow ⬆ & ROI better perfused and supplied.

c) Vessel permeatibilty ⬆ in elevated temperatures

Why is Hyperthermia beneficial to Chemotherapy ?

e) HT ➒ partial demontage of cytoskeleton: enlarged tumorpores
➒ facilitated uptake of chemotherapeutical

Summary Rationale

* augment transport of cytostatica to ROI
(blood circulation , vascular permeability etc.)

* facilitate metabolism

How to combine CTX and HT?

Unfortunatly reasearch only just beginning ; not yet sufficient data and consensus.

I timewise coordination

already some consens on

* Doxurubicin	HT during or imm. after infusion
* Cisplatin	1 - 2 h before infusion ?
* Gemcitabine	HT in 24 hours difference 2)

II advised temperatures

in tendence likely moderate HT in the range of up to 40,5 ^{0}C 1)

1) **Joan M.C.Bull** et al: Fever range whole -body thermal therapy combined with cisplatin , gemcitabine and daily interferon-alpha: A descriptiion of a phase I -II protocol , ,int J.Hyperthermia 2008: 24(8):649 -662
2) **Satoko Adachi** et al: Effects of hyperthermia combined with gemcitabine on apoptotic cell death in cultured human pancreatic cancer cell lines , Int.J.Hyperthermia 2009 25(3):210 -219

Chemotherapeutica (CTx) and Hyperthermia (since 1981)

Effect	Potentiated by heat	Unaffected by heat
Linear increase	Etoposid (➔24 h HT)	
Linear increase	Cisplatin *	Hydroxyurea
	Carboplatin *	Methotrexate
Linear increase	Mitomycin C *	Vinblastin
> linear increase	BCNU * /ACNU	Cytarabin
Linear increase	Cyclophosphamide	Floxuridin
	Bleomycin *	Acitnomycin
> linear increase	Melphalan *	Etoposid
Exponential	Adriamycin	PALA
	Epirubicin *	Taxane
	Dacarbazin	
Linear increase	Ifosfamid *	
	Lomustin Nimustin	
	Temozolomide	
> linear increase	Mitoxantron / Vepesid	
Linear increase	5- FU Bendamust	
> linear increase	Doxorubicin / Gemcitabine (<== 24 h HT)	

* Verified in clinical studies

Biological effects of HT

CELSIUS

Biological Effects of loco-reg. Hyperthermia				Roesch 2014	CT = Chemoth. IR = Immunresp.	
Physiological Criteria	**Effect**	**@ 38-40 °C**	**@ 40,5-43°C**	**Rational**	**Sensitzer to**	**Ref.**
blood flow in medium/ larger vessels	cooling to neighb tissue rel.less pressure; slower flow	+ -/+	+ -/+	heat into region of interest incr. supply of agents, O_2, lymphocytes	CT,RT, IR	
blood flow in microenvironment	first increasing then chance to collaps	++ +	- ++	perfusion improves agent delivery when collaps-> heat peaks !	CT,RT, IR	Hill
vascular permeability	enlarged	+	++	increased migration into matrix	CT, RT	Horseman
oxygentation	at high temp. rev. effect in Δ t !	++	-- ++	contraindicated if HT is before RT more flow, better access into matrix	RT O_2 dep. agents	Vaupel Song
interstitial pressure	reduced	+	+	facilitate trafficking leuco- & erythrocytes & agents	CT, RT, IR	Chen Reparsky
ATP	further energy depletion (increased metabolism)	+	++	contributes to apoptosis (intensifd. hydrolysis; breakdown to glycolysis)	CT, IR	Gerweck
intracellular pH	increasing	+	++	however protects from damage x/γ rays	CT	Vaupel
extracellular pH	decreasing	+	+	better lymphocyte trafficking	IR, CT	Vaupel
metabolism	increasing	+	+	pharmakokinetic acceleration	CT	
HSP (heat shock proteins)	if inside cell : protect cell if outside expr.: apoptosis	+	++	effective natural boost to immune resp.	IR	Srivastava Onishi
calrecitulin	protein exposed at cell membrane after heating	+	+	serves as eat-me signal to immune system	IR	Obeid Gaipl
DNA repairs	inhebited /retarded	+	++	due to heat stress after radiation best applied HT closly after RT	RT	Sapareto RotiRoti
S2 cell cycle	prolonged	+	++	sensitizer to RT	RT	Amaya
Abscopal effect	RT induced immune modul.	+	++	effect on distant metastasis	RT, IR	Demaria
immune modulation	increased (best @39-40,5 oC)	++	+	natural body function for innate (NK cells) + adaptive immune system	IR	Multhoff Reparsky
pain relief	reliefs neurological pains	++	+=	mechanism not yet fully understood		Sridar

Hyperthermia as wave resonance / EM fields

CELSIUS 42



?

Hyperthermia
as direct cyto - static cell death
due to characteristics of the EM Field
and/or resonances

It still is speculation.

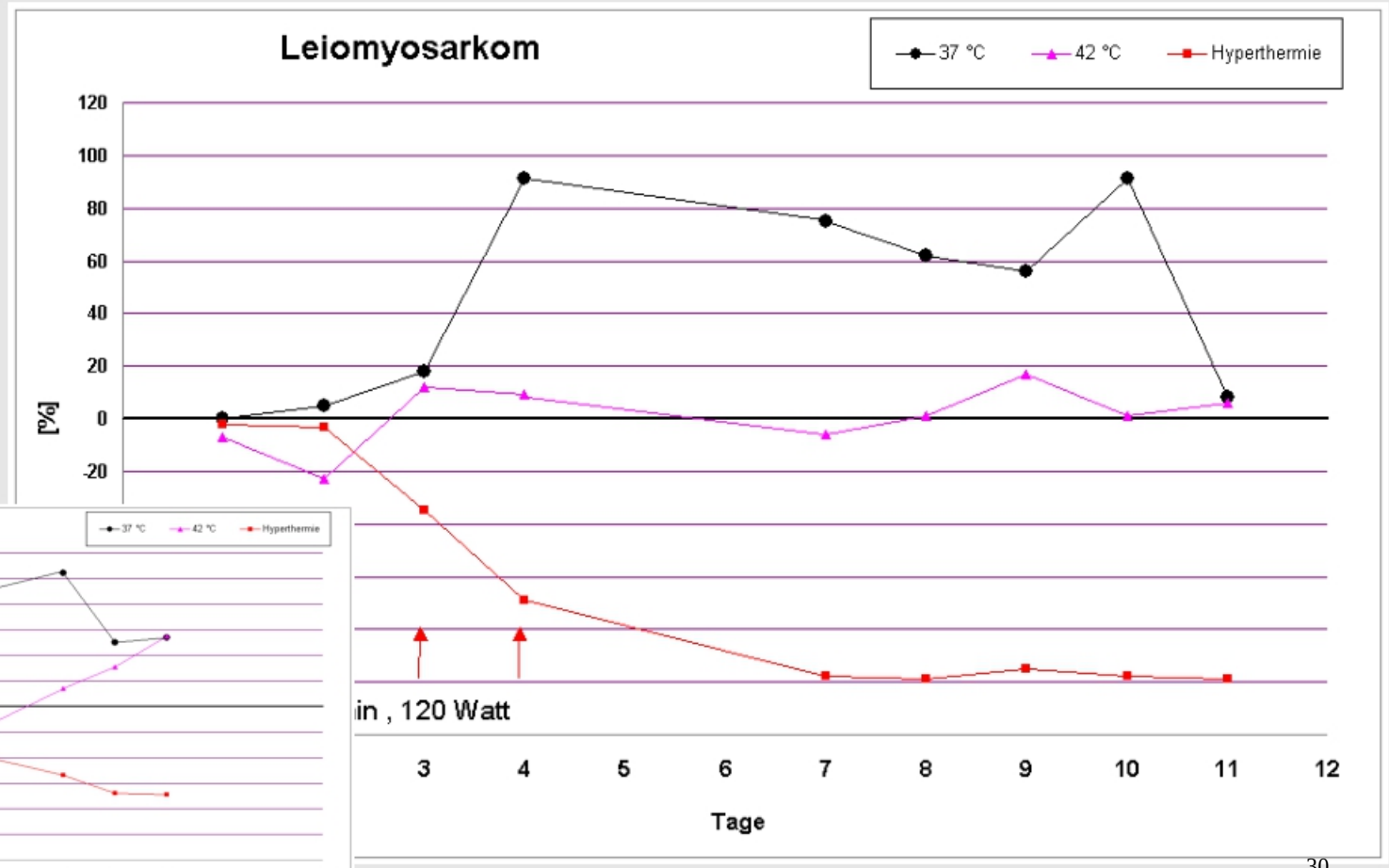
Despite RIFE ´s work

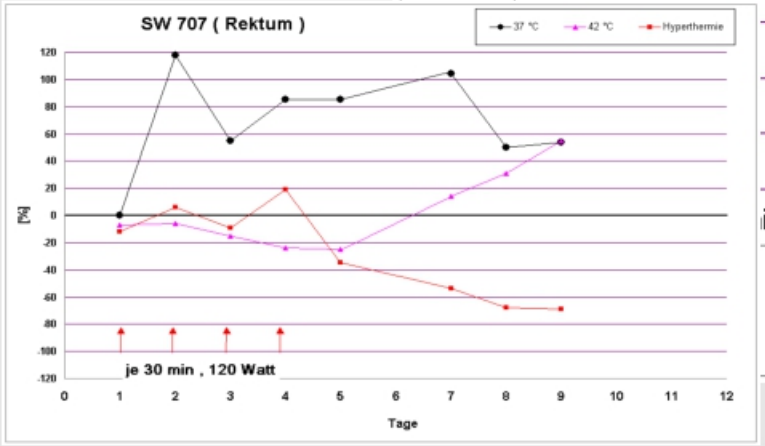
We tried for years now (so far in vain)
to find reproducable resonances to mailgne cells

Hyperthermia as wave resonance / EM fields



Hyperthermia as direct cyto - static cell death due to characteristics of the EM Field and/or resonances





Another Novel Development: Non-toxic therapies combination

Regional Hyperthermia+PDT(Photodynamic Therapy)+Immunotherapy



Grasp the potential !

Celsius42+ capacative deep region hyperthermia at ~13 Mhz
with bidirectionally active adjustable electrodes :

a. Well capable of generating sufficient in -depth temperature impact !

b. Well beneficial to complement radiation therapy & many chemotherapy !

c. Well immunological activation to tumor cells

希伯克拉底：給我熱 我將治療一切的疾病

平安 健康 順心

Thanks for your attention!









Wide consensus in ESHO on a hyperthermia session :

CELSIUS 42

· An effective Hyperthermia session needs a sufficient temperature gradient (e.g. SAR + 1,0 ^{o}C in 5 min)

· Temperature should reach min. 40 -42 ^{0}C for > 50 % of the session (e.g. 10 CEM 43 ^{o} C T_{90})

however this may need to be differentiated !

· Respective quality control is highly desirable

Principal of Hyperthermia impact in capacitive system of Celsius42

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Device: TCS – Tumor Cell Solution
Frequency 13,56 MHz
15 – 600 Watts input power
two actively sizable electrodes





Heating Principle: two adjustable electrodes
patient ´s body = dielectricum

Benefit of Hyperthermia.

This document aims to give an overview of the possibilities and current state of science in the application of regional hyperthermia. The information shown is part of the current approval of the TCS - Tumor Cell Solution and is continuously reviewed and supplemented.

There are several forms of hyperthermia. These are to be considered as different tools for different requirements. The following data are based on regional hyperthermia.

R egional hyperthermia has proven its benefit in a variety of scenarios.

Let us differentiate in two dimensions:

a. HT augments the effects of radiation therapy. It makes radiation more effective! HT can also enhance the effects of most chemotherapies. It accelerates metabolism in the Region of Interest and is still considered a systemic therapy. Finally HT contributes to the new immune therapies and is in effect an immune therapy itself. For all these effects ample evidence can be found in literature.

b. R egional h yperthermia is best suited for r egional tumors. These can be solid primary tumors or metastas es.

Prominent trials give evidence for cervix, prostate, pancreas, colon, rectum, liver, tumors in peritoneum, lungs, mama, esophagus, head and neck, brain tumors and soft tissue sarcoma , melanom a, non -Hodgkin tumors. R egional hyperthermia is not used for hematologic tumors (blood cancer) .

Limits of hyperthermia are with organs of high perfusion such as kidney (interesting ly, to note that pancreatic cancer shows very good response rates to HT) and adipose patients with thick fat layers are also difficult to heat up in the depth of the bod y.

In the tables below, we show a selection of results, which led to the outcomes shown in the studies. This data is constantly supplemented by new data from studi es and shows only a selection of thousands of studies on hyperthermia worldwide.

Your Celsisu s42 Team

Excerbt of publications and results

The efficacy rates of hyperthermia in combination with radiotherapy and / or chemotherapy for various types of cancer is exemplified by 37 publications. The results should shed light on the positive aspects of hyperthermia therapy in combination with radiotherapy and / or chemotherapy for various types of tumors.

Tumor Site	Overall response % without hyperthermia	Overall response % plus hyperthermia treatment	Studies
Cervix cancer	46	66	Datta NR 1987
Cervix cancer	35	72	Hornbach NB 1986
Cervix cancer	53	83	Harima Y 2001
Cervix cancer	50	85	Harima Y 2001
Cervix cancer	50	80	Harima Y 2000
Colorectal cancer	10	43	Hiraoka M 1984
Colorectal cancer	36	54	Nishimura Y1992
Colorectal cancer	0	11	Goldobenko GV 1987
Colorectal cancer	55	71	Savchenko NE 1987
Colorectal cancer	20	100	Hamazoe R 1991

Tumor Site	Overall response % without hyperthermia	Overall response % plus hyperthermia treatment	Studies
Oesophagus cancer	25	63	Muratkhozhaev NK 1987
Osophagus cancer	19	41	Sugimachi K 1994
Oesophagus cancer	24,2	50,4	Kitamura K 1995
Oesophagus cancer	8	70	Sugimachi K 1992
Oesophagus cancer	8	27	Sugimachi K 1992
Oesophagus cancer	59	81,2	Wang J 1996
Rectal cancer	33	69	Tsyb AF 1987
Rectal cancer	5	23	You Q-S 1993
Superficial carcinoma	62,6	82,8	Egawa S 1989
Superficial tumor	25	46	Lindholm CE 1987
Superficial tumor	63	88	Uozumi H 1986
Subcutaneous carcinoma	59	83	Jo S 1994
Malignant melanoma	28	46	Overgaard J 1996
Malignant melanoma	39	72	Kim JH 1982
Lung cancer (Whole body hyperthermia)	36	68	Engelhardt R 1989
Lung cancer (non-small cell)	20	73	Karasawa K 1994
Pancreatic carcinoma	47	68	Maluta S 2008
Pancreatic carcinoma	14	57	Takagi T 2008
Glioblastoma multiforme	15	31	Sneed PK 1998

Table: Efficacy rates of oncologic thera py with and without hyperthermia

A rough look at the efficacy rates of oncologic therapy without and with hyperthermia shows: without hyperthermia an average therapeutic efficacy rate of 35 % is achieved (regarding different efficacy parameters), while therapy plus hyperthermia amounts to 64 %. Since there are 37 different publications that were created under different conditions and the patient population cannot be homogeneous, the figures are comparable to a limited extent only . The publications and thus also the collected data originated over a period of 30 years, from 1978 to 2008.

*Excerpt from the clinical evaluation file 2018

Your Celsius42 Team