Basic principle and new results of Oncothermia

Prof. Dr. Andras Szasz

Professor of physics & biophysics
Chair, Department of Biotechnics, St. Istvan University, Hungary &
Visiting professor (bioelectromagnetics) in Pazmany P. Catholic University, Hungary &
Visiting professor (fractal physiology) in Chiba University, Japan &
Chief Scientific Officer (CSO), Oncotherm GmbH, Troisdorf, Germany

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Korean Oncothermia Study Group
(KOSG'17)
Daejeon area cancer center

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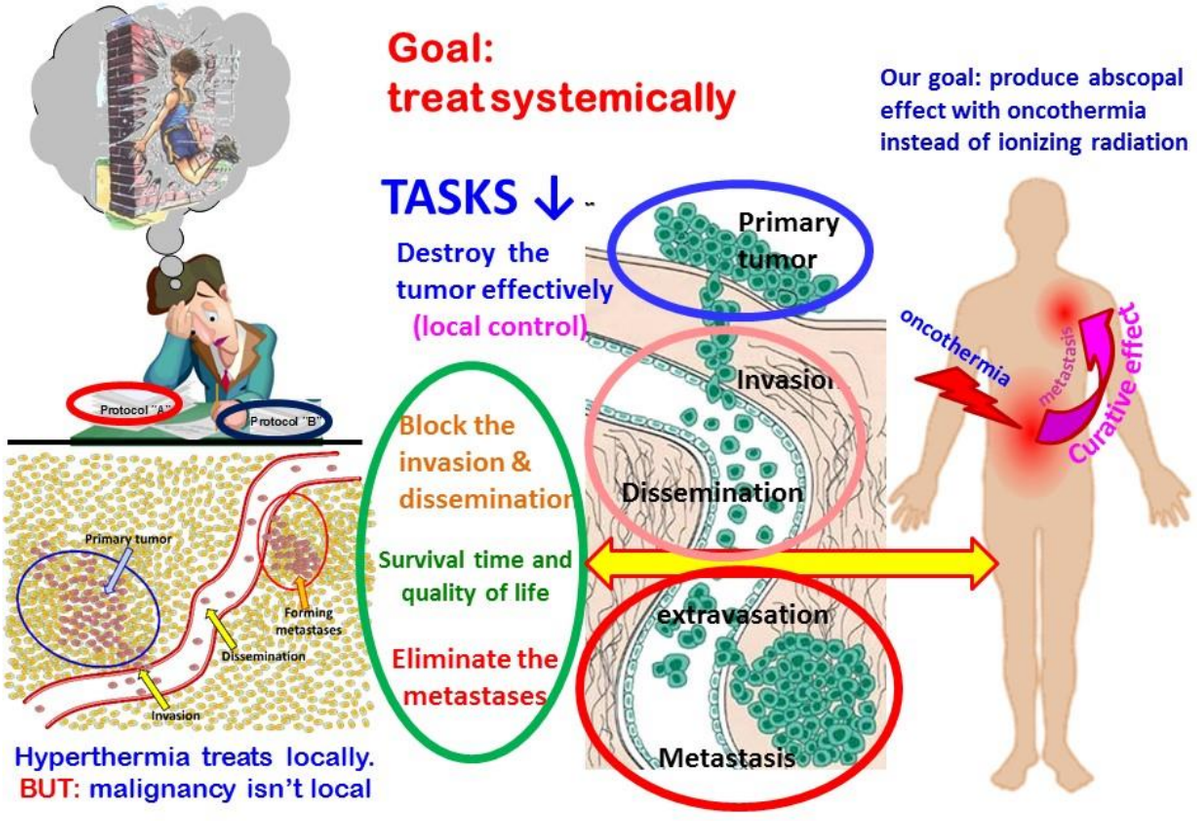
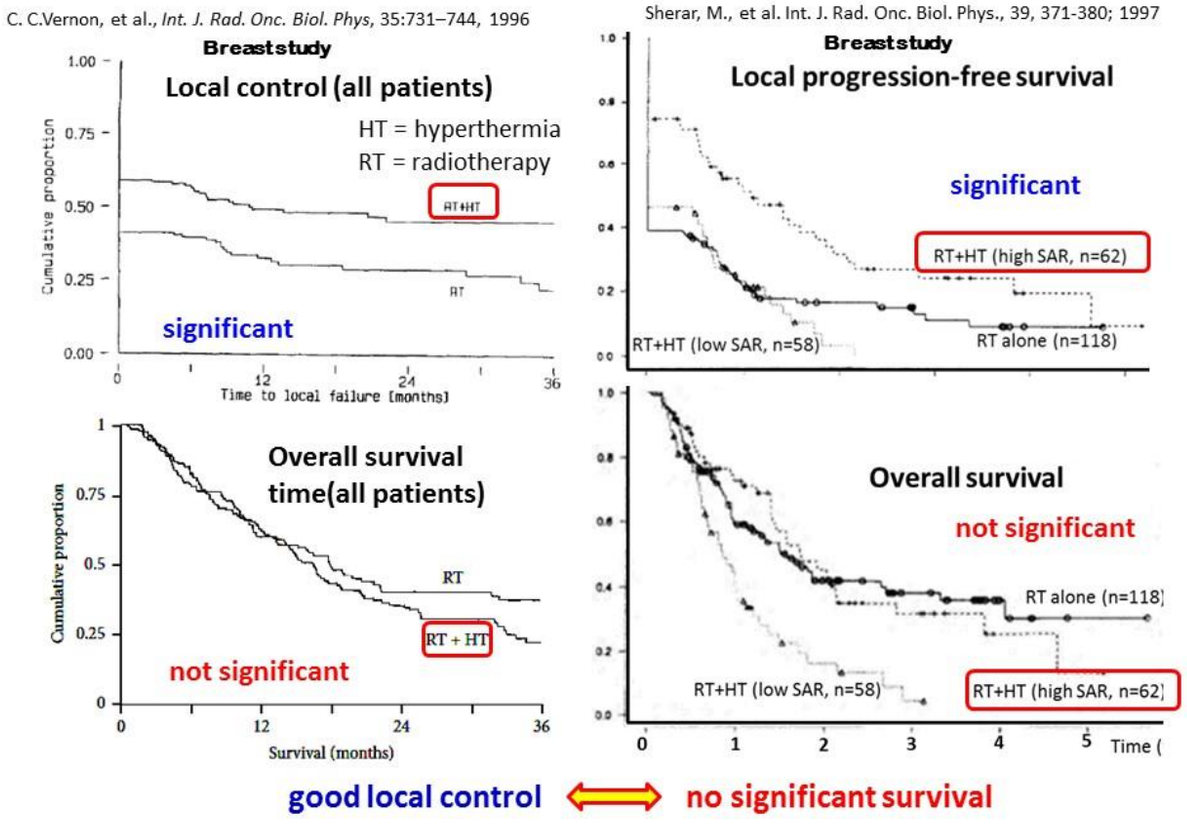
Outline

- ❑ Challenges (hyperthermia at crossroads)
- ❑ Oncothermia basic principles
- ❑ Oncothermia new results
- ❑ Breakthrough perspectives
- ❑ Take-home messages

Challenge in oncology – what to treat?



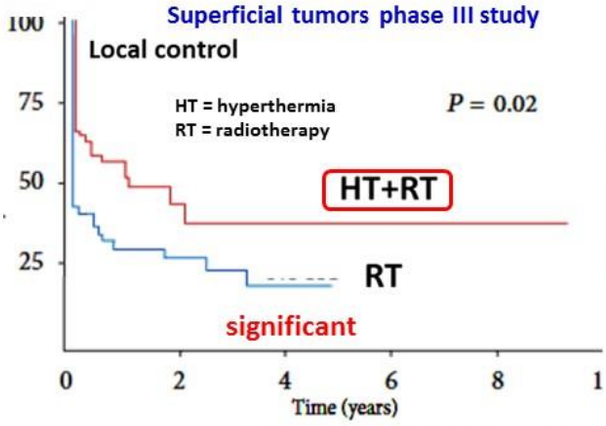
Local control and survival time are not in harmony

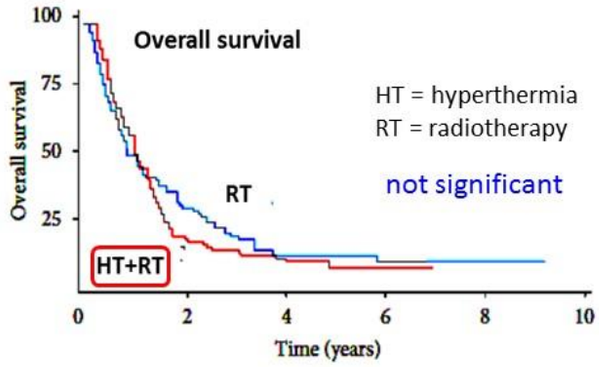


Local control and survival time are not in harmony by conventional hyperthermia

Superficial tumors phase III study

Jones EL, et al.; J Clin Oncol. 23:3079-85, 2005





Overall survival of **easy heatable surface tumors** is **also not improved by conventional hyperthermia**

Non-small-cell lung cancer

Michihide Mitsumori, et al; (2007) Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers:, Int J Clin Oncol (2007) 12:192–198

Initial site of disease progression after treatment

	RT (n = 40)	RT + HT (n = 40)	P-value
No recurrence	3	4	
Primary tumor and/or regional lymph nodes	15	7	
Distant metastasis	2	10	0.07
Both locoregional and distant[a]	3	4	
Unknown/missing	17	15	

[a] Patients in whom the interval between locoregional disease progression and distant metastasis was less than or equal to 1 month

Distant metastases are induced by conventional hyperthermia

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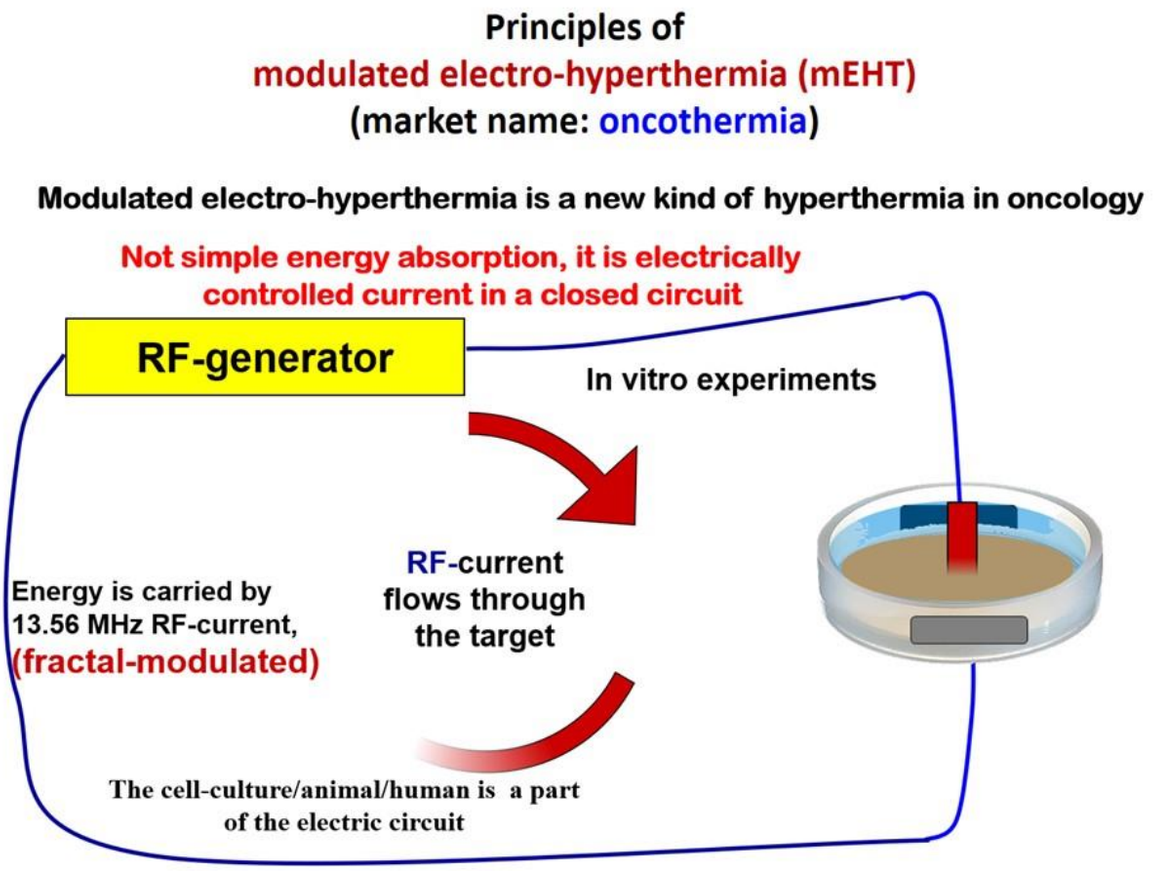
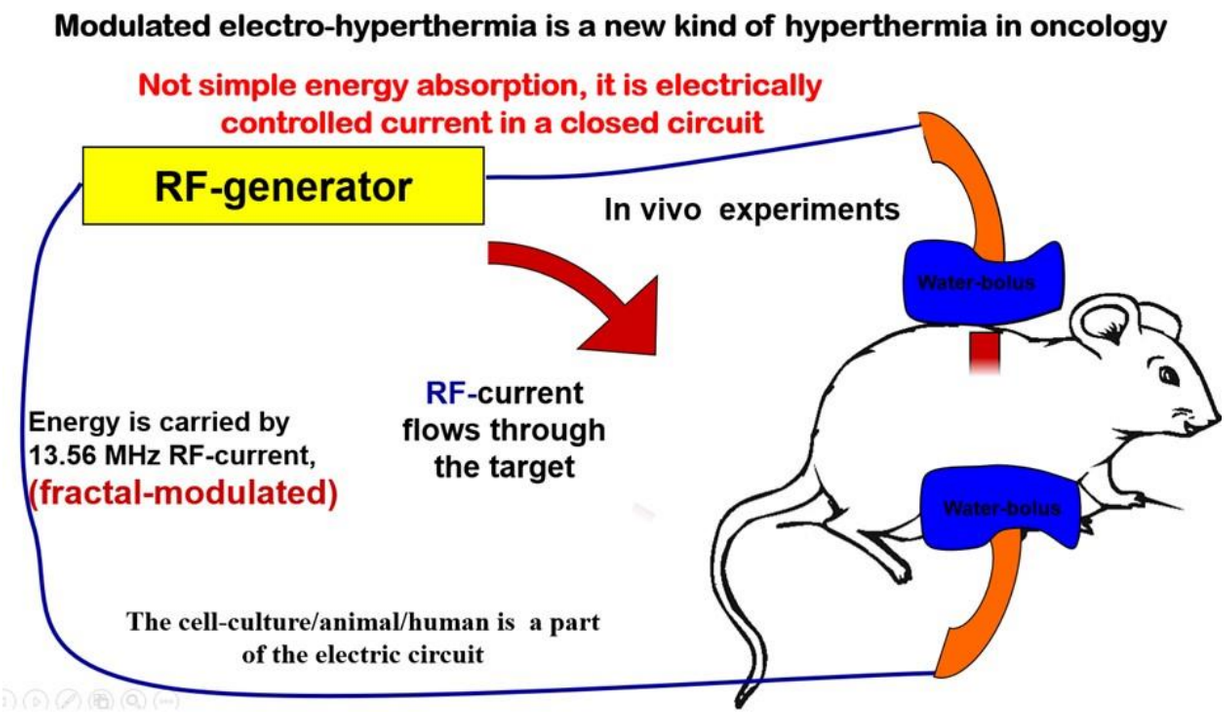
- ❑ **Take-home messages**


Principles of
modulated electro-hyperthermia (mEHT)
(market name: oncothermia)
Modulated electro-hyperthermia is a new kind of hyperthermia in oncology
Not simple energy absorption, it is electrically controlled current in a closed circuit
RF-generator
In vitro experiments
RF-current flows through the target
Energy is carried by 13.56 MHz RF-current, (fractal-modulated)
The cell-culture/animal/human is a part of the electric circuit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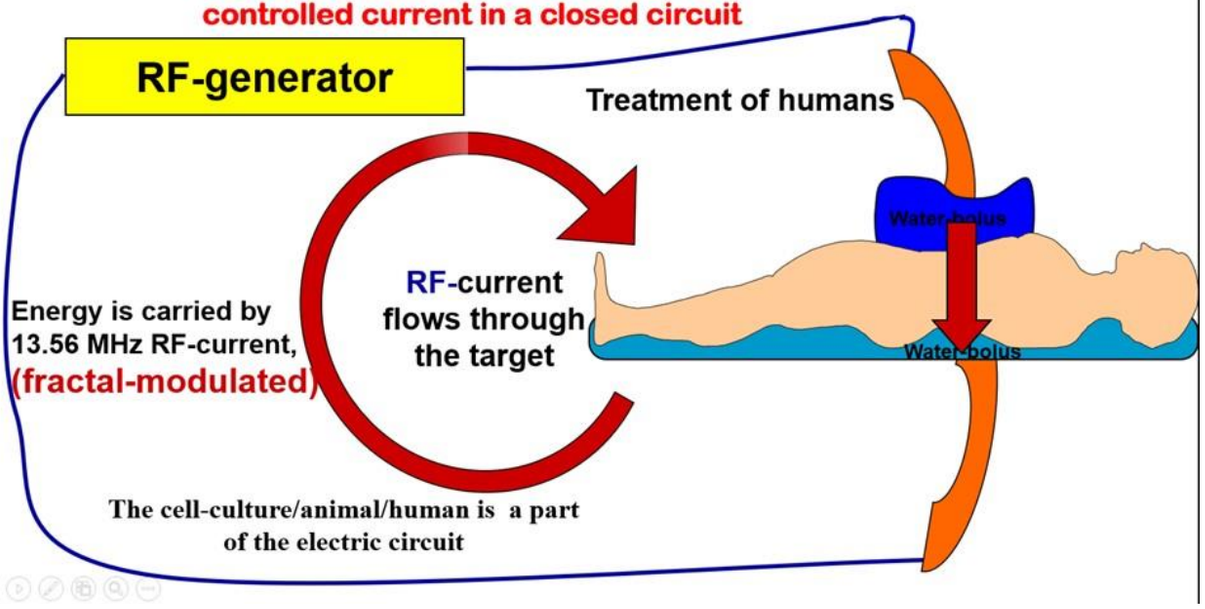
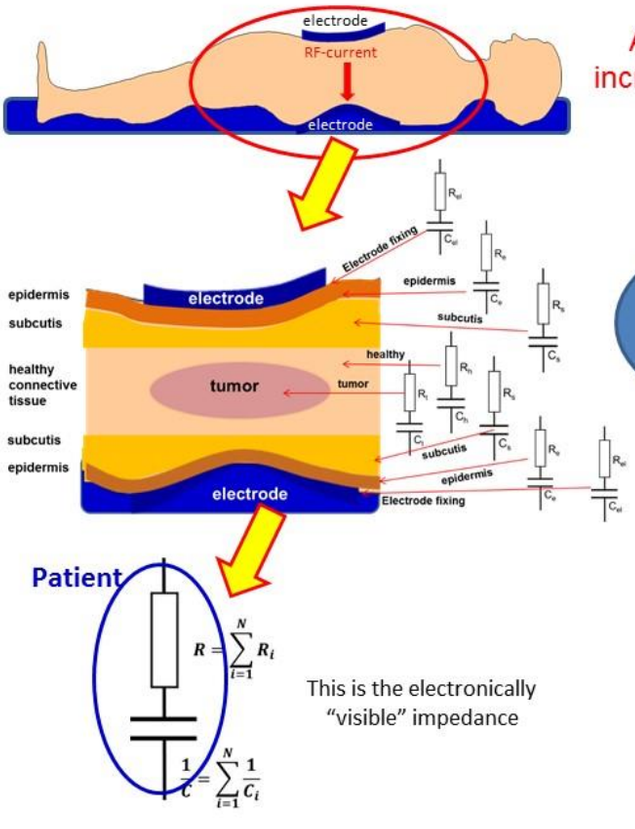
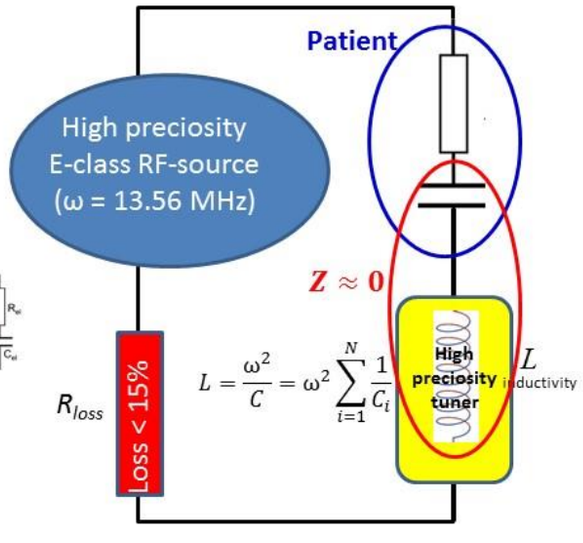


Technical renewal



This is the electronically "visible" impedance

Apply serious impedance matching to increase the energy absorption and control the living dynamics by electric way



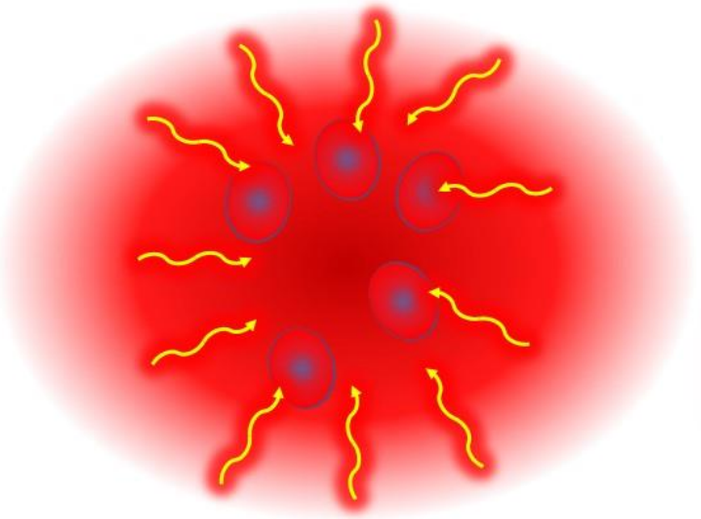
Patient is an electric part of a precisely tuned resonant circuit

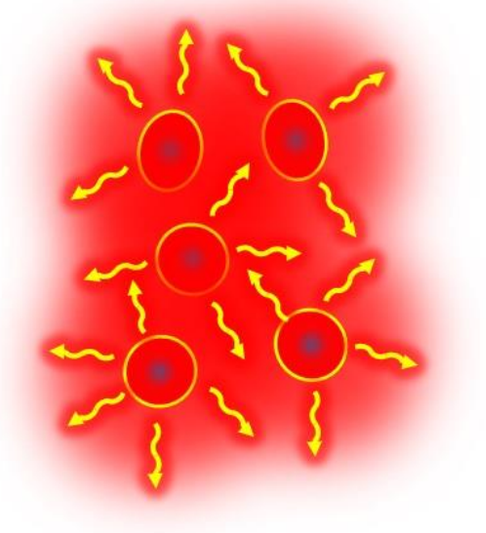
Control of the blood-flow

Instead of homogeneous heating heat heterogeneously, induce blood-flow by indirect heating into the fever range

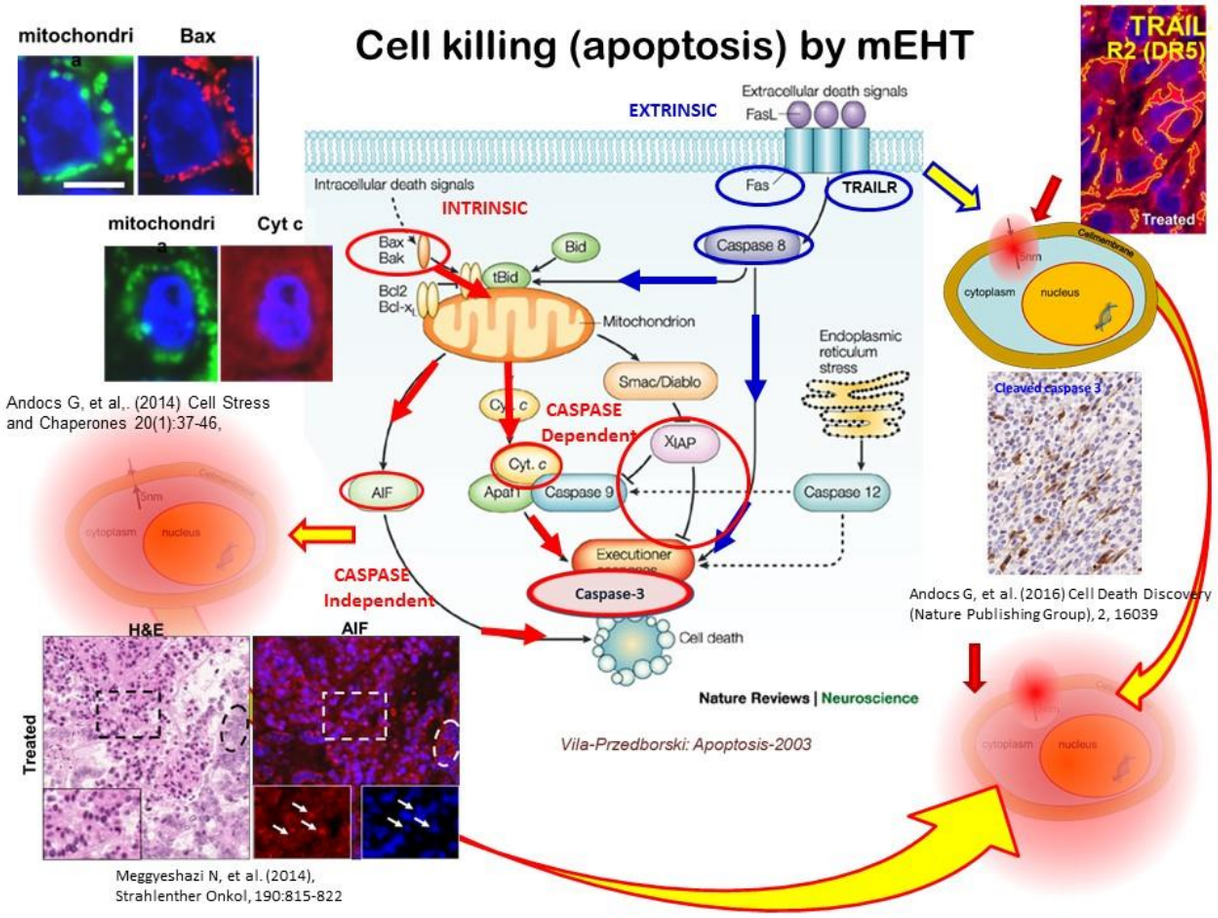
Conventional hyperthermia
heats the complete mass of the tumor isothermally by radiation + convection + conduction

Oncothermia
heats selectively, heterogeneously targets the malignant cells only



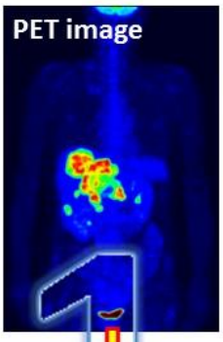


Contrary to conventional heating oncothermia heats from inside, like nanoparticles do



Selection of the malignant cells by oncothermia

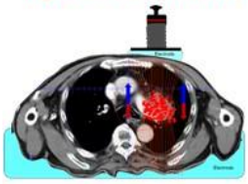
Selects the tumor



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

High ionic concentration

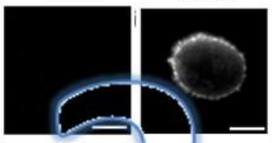
High electrical conductivity



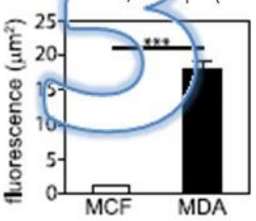
Selects the malignant cells

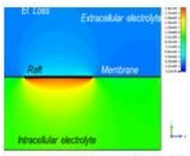
Energy absorption on membrane rafts

Non-tumorigenic (MCF) Metastatic (MDA)



Epifluorescence microscopy (EFM)
Staunton JR et al; Sci.Rep.3 (2008)

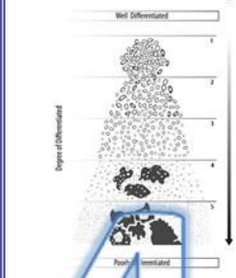




E. Papp, et.al. OJBYP, 2017

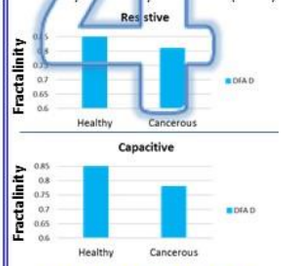
Modulation (fractal physiology)

J.A. Llanos-Pérez; 2015



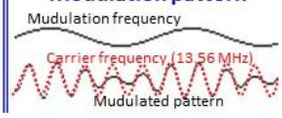
Selection by pattern

Loveluck et Al. Phys.Rev. E 76 (2007)



Modulation pattern

Mudulation frequency



Targeting consequences

Oncothermia membrane-selective heating

Inhomogenous, non-equilibrium heating below cytotoxic temperature

↓

Heat induced signal transduction pathways resulting apoptosis

↓

No protein denaturation occur

↓

Damage Associated Molecular pattern (DAMP)

↓

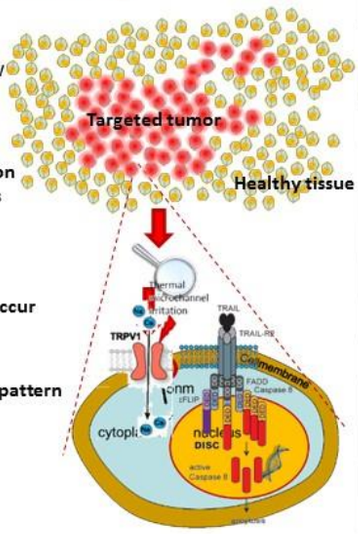
Tumor antigens became recognizable

↓

Immunogenic cancer cell death (ICD)

↓

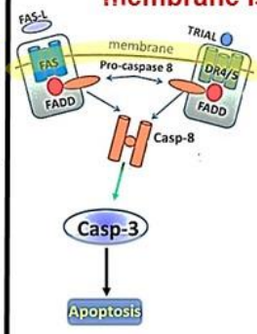
Good basis for immunotherapy combinations



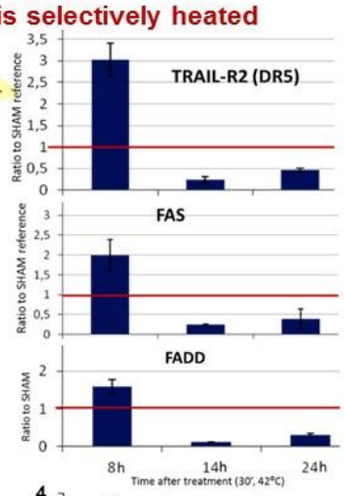
It is thermal excitation, proven by Arrhenius plot

Meggyeshazi N. Andocs G. et.al. – DNA fragmentation and ..., Rad. &.Onc. 2014

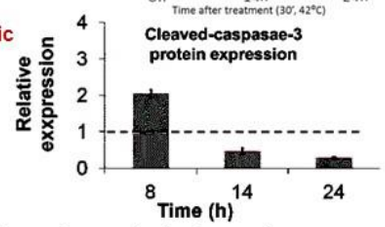
Dominantly apoptosis, which uses external pathways, because the cell membrane is selectively heated



Death-receptors are activated
(8 h after the treatment)



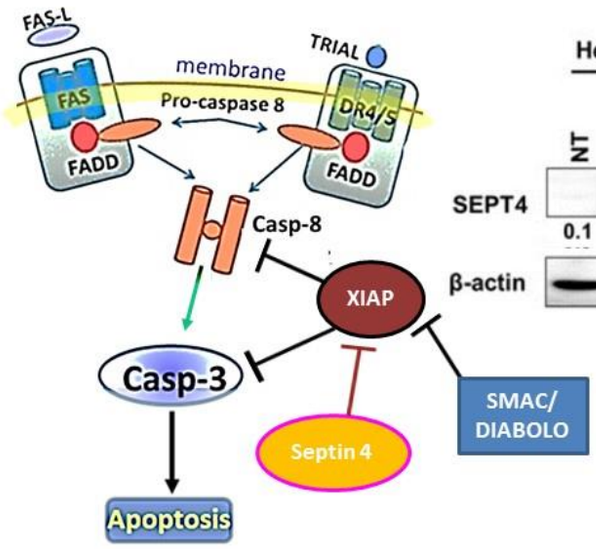
(external apoptotic pathway)

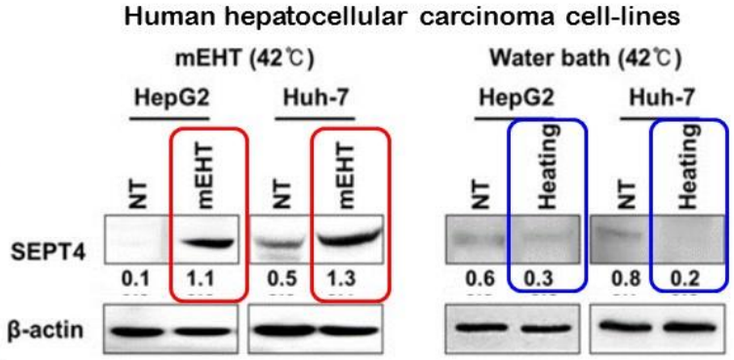


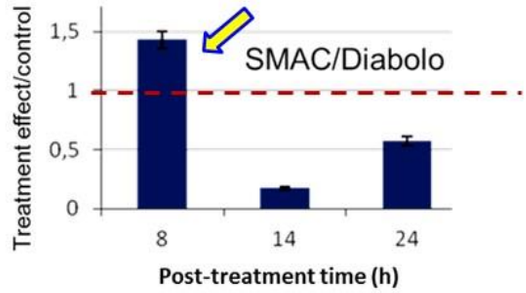
Meggyeshazi N. PhD theses, Semmelweis University, Hungary

Oncothermia is based on apoptotic effect in vivo

The enemy of my enemy is my friend





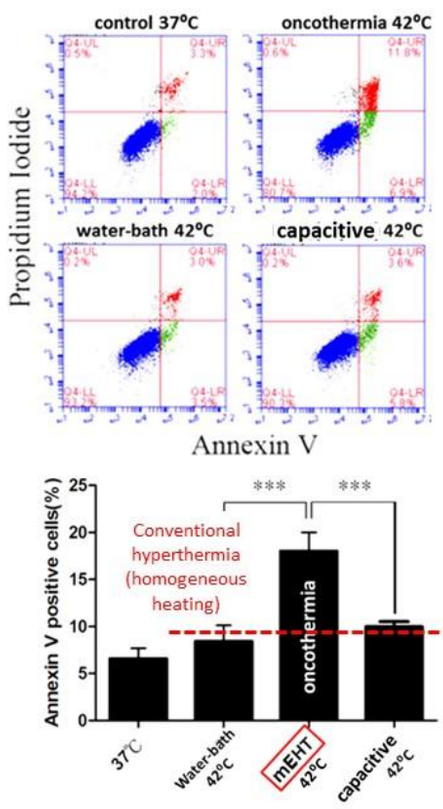


Tae-Won Jeon, Heebum Yang, Chang Geol Lee, Sang Taek Oh, Daekwan Seo, In Hye Baik, Eun Hye Lee, Ina Yun, Kyung Ran Park & Yun-Han Lee; (2016) Electro-hyperthermia up-regulates tumor suppressor Septin 4 to induce apoptotic cell death in hepatocellular carcinoma, Int.J.Hyperthermia, http://dx.doi.org/10.1080/02656736.2016.1186290

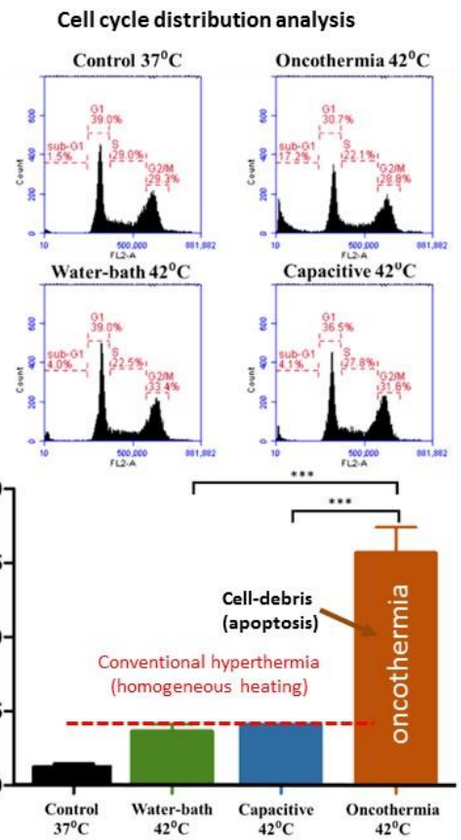
Meggyeshazi N, Andocs G, Balogh L, et al. (2014) DNA fragmentation and caspase-independent programmed cell death by modulated electrohyperthermia, Strahlenther Onkol, 190:815-822

Apoptosis

HepG2 cells (in vitro)



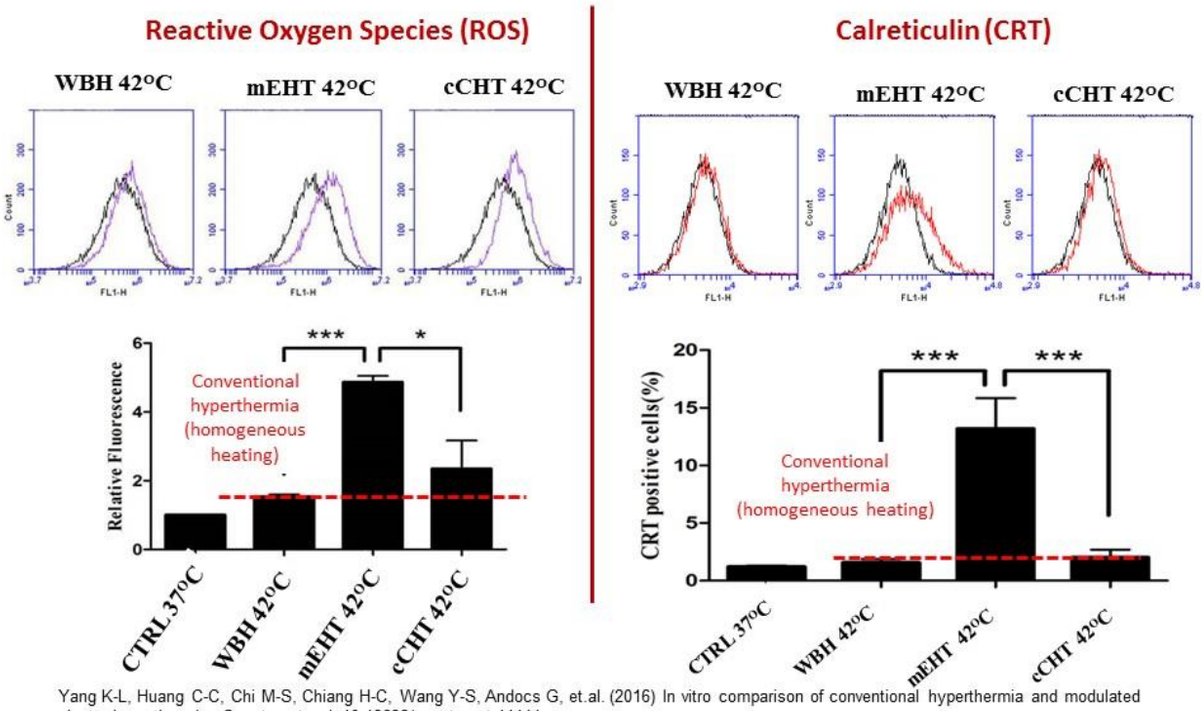
Tsang Y-W, et al, Improved Immunological Tumor Microenvironment by Combined Electro-Hyperthermia followed by Dendritic Cell Immunotherapy; Cancer Immunology, Immunother 2015



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

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

We used flow cytometry to detect ROS and CRT on the surface of hyperthermia HepG2 cells.



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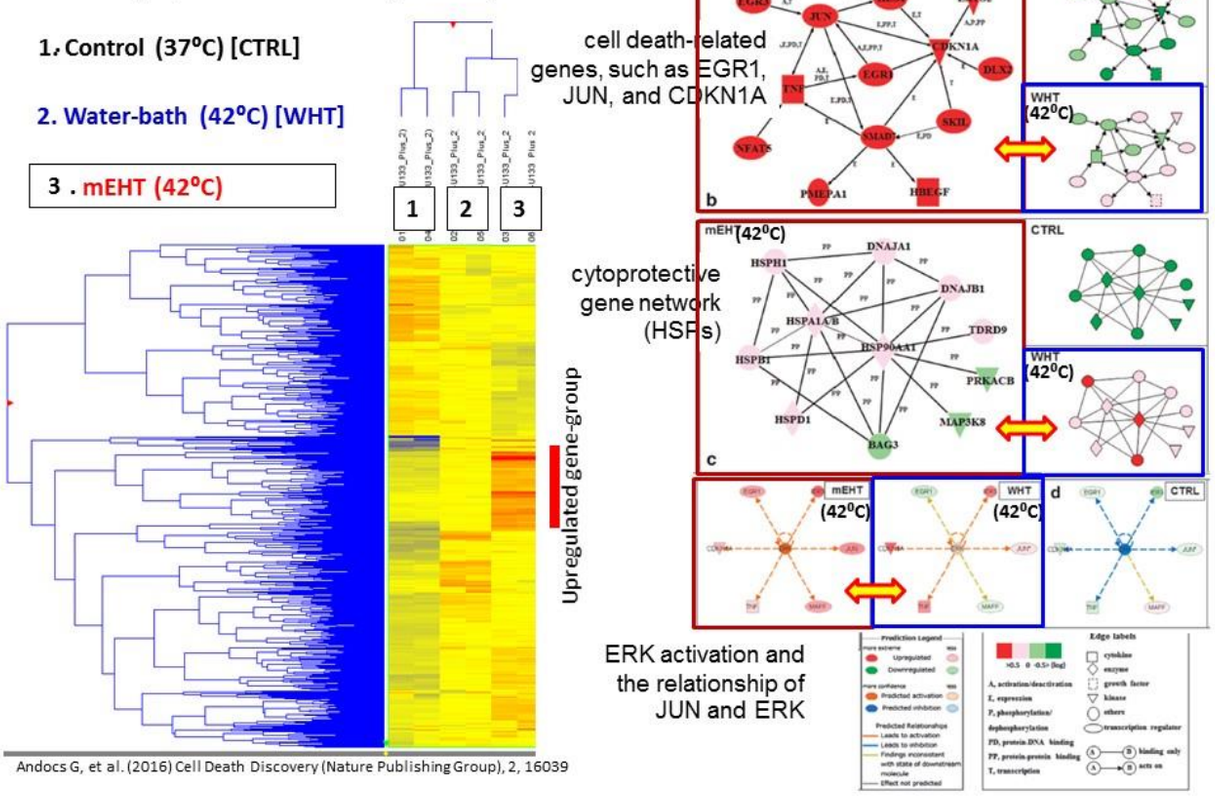
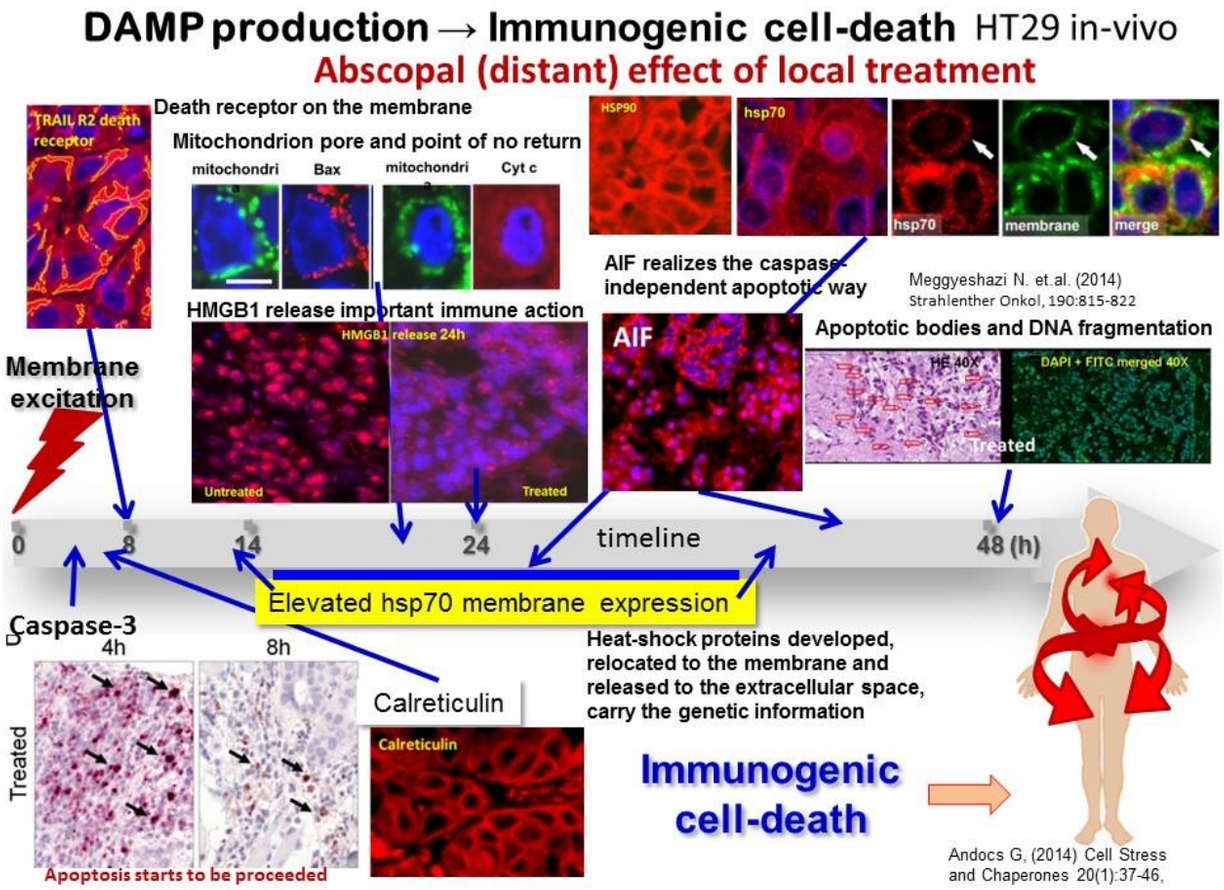
mEHT heats differently (mRNA-based info)

Human lymphoma U937 cell (**in-vitro**)

1. **Control (37°C) [CTRL]**
2. **Water-bath (42°C) [WHT]**
3. **mEHT (42°C)**



Andocs G, et al. (2016) Cell Death Discovery (Nature Publishing Group), 2, 16039



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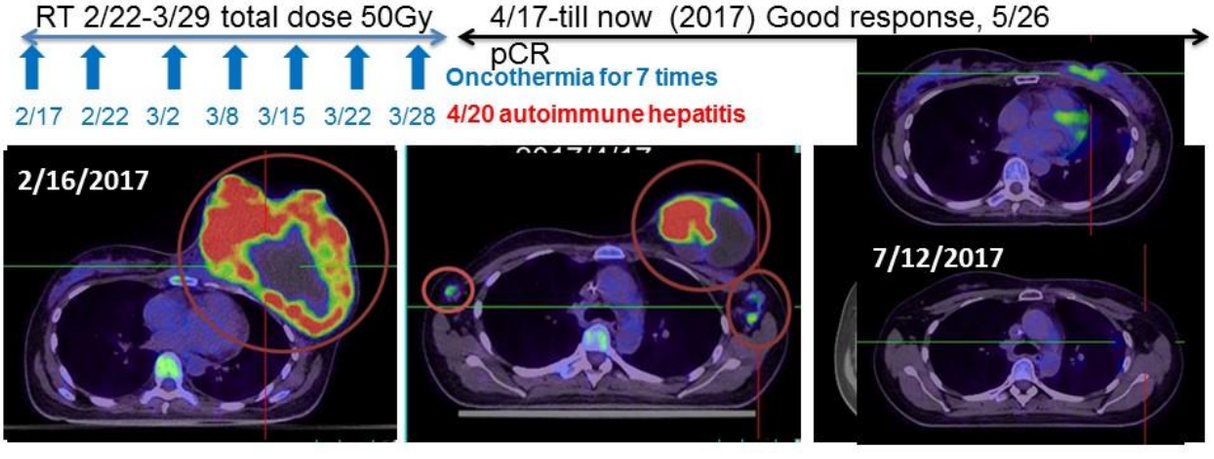
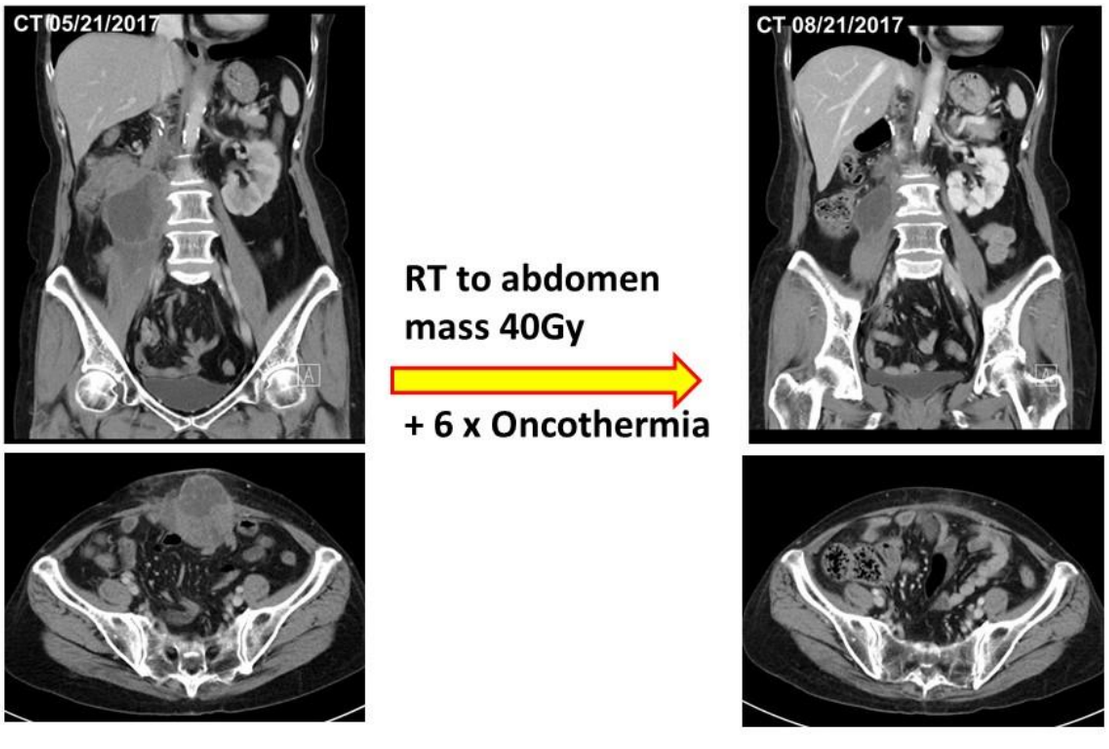
Triple negative locally advanced breast cancer

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (unpublished yet)



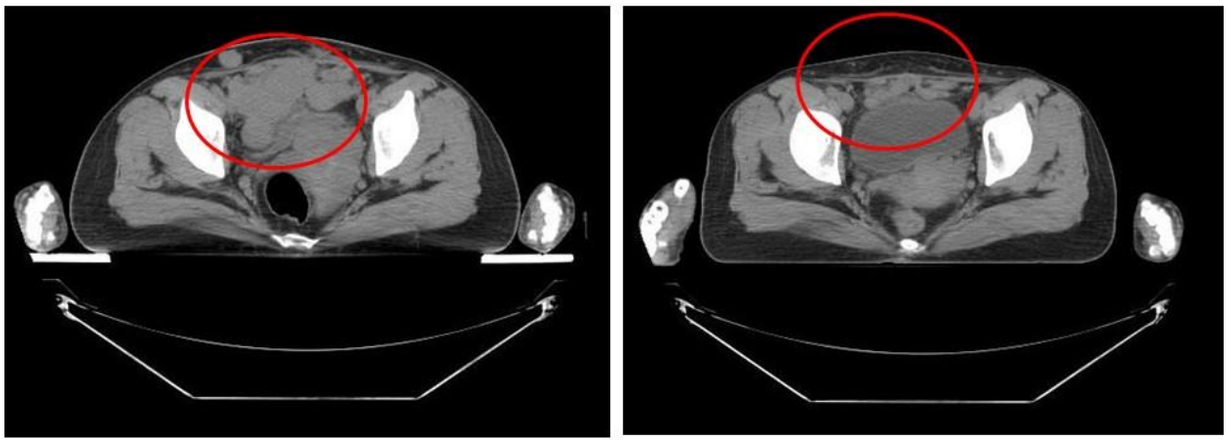
Urothelial-cell carcinoma of renal pelvis with abdomen and liver metastases

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)



Recurrent uterine sarcoma with peritoneal seedings, refractory to chemotherapy

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

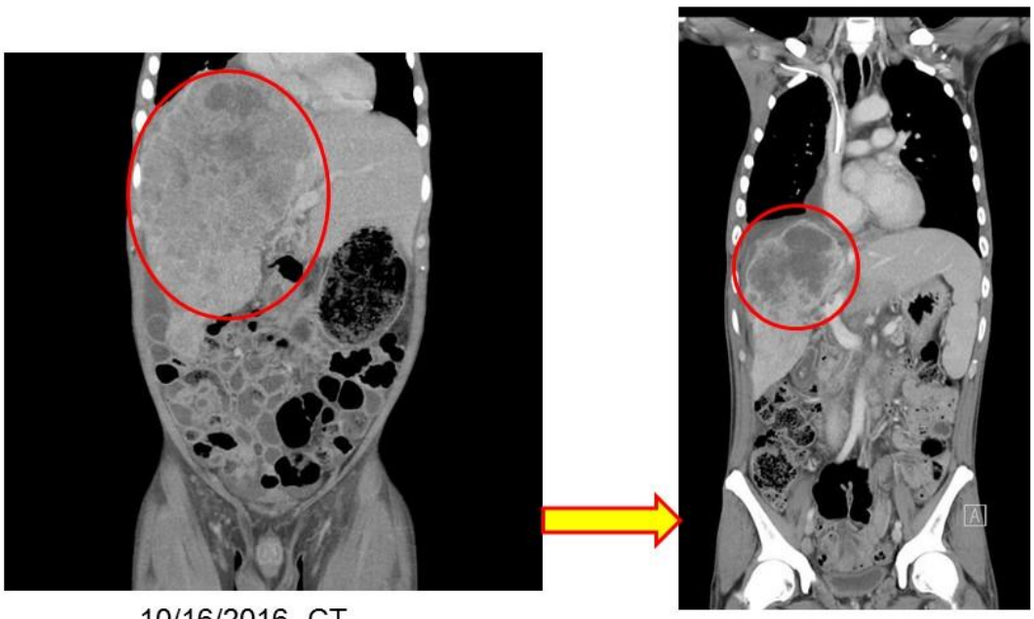


Before treatment → After tretment

salvage with combined radiotherapy (45Gy/30fx) intratumoral injection 2.5 mg ipilimumab, i.v. nivolumab 50mg and oncothermia 6 times (1 time/week).

Advanced hepatoma

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)



10/16/2016 CT

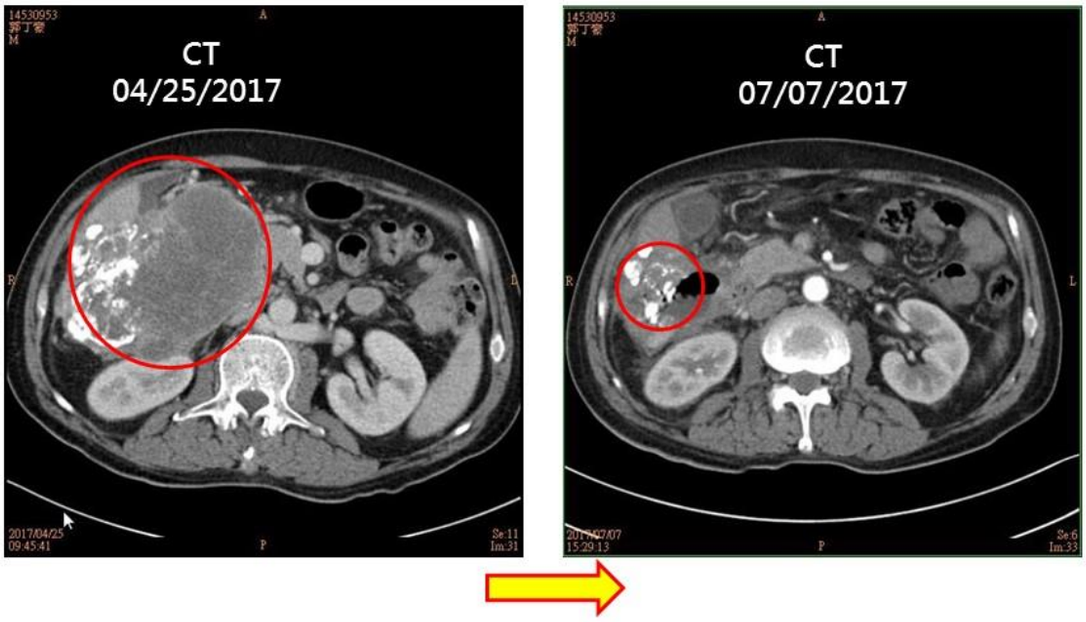
05/25/2017 CT

Keytruda 50mgQ3W +
Lipodox 20mg Q2W
+ liver radiotherapy

Oncothermia for liver 15 times

Hepatocellular carcinoma (HCC)

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)



RT 46 Gy/23fx + weekly Oncothermia x 5 + Lipodox 20mg x3

Cholangiocarcinoma

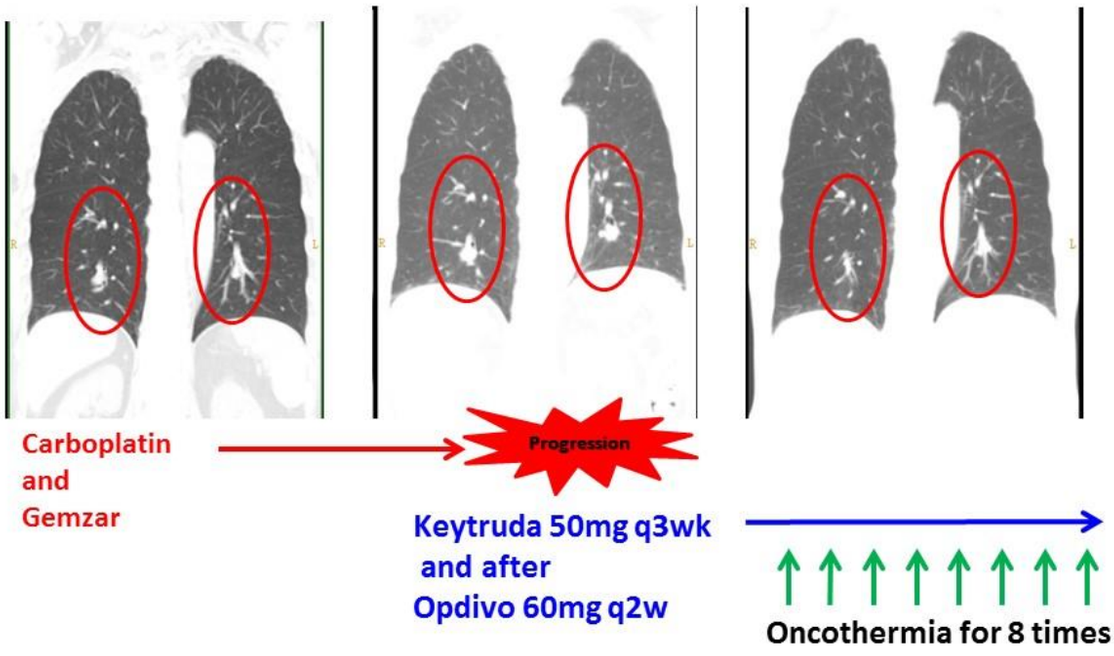
Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

D1: Avastin 200MG
D2: Gemzar 500MG/M2 , D2~D4: 5-FU 500MG/M2
D5: Keytruda 150mg
RT (Cholangiocarcinoma): from 6/15 to 7/5, total 30Gy/15Fx.
Oncothermia : from 6/28 to 7/31, total 10 times

Bladder Cancer with Lung Metastasis

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

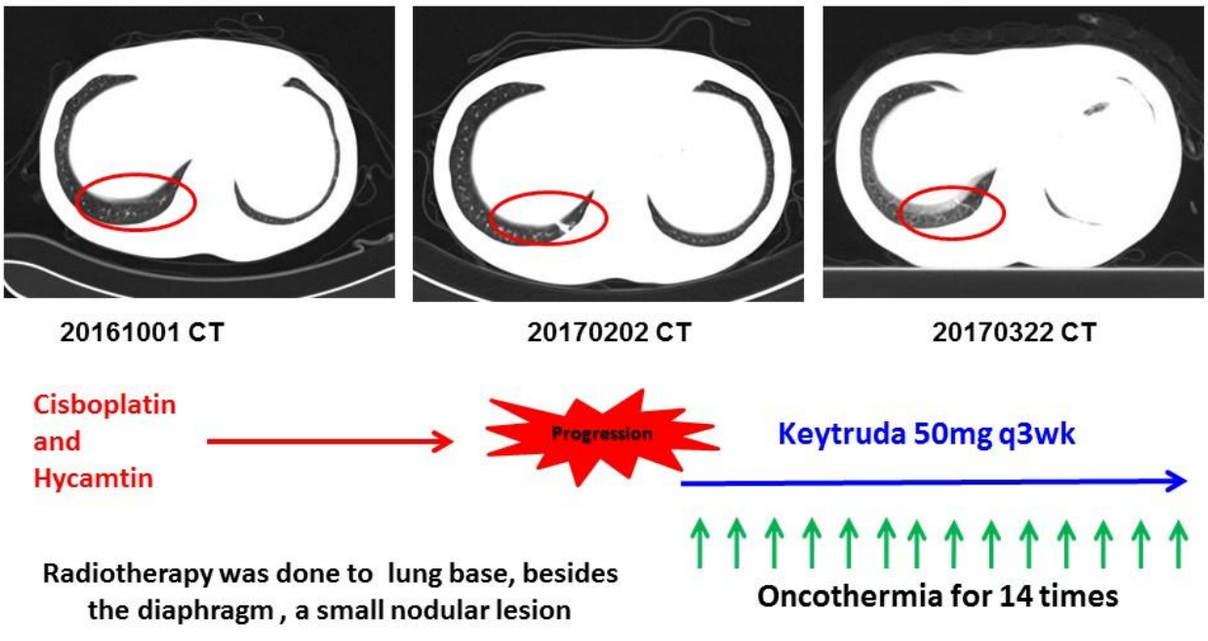
Anti-PD1 complementary to oncothermia



Small Cell Lung Cancer with multiple Bone Metastasis

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

Anti-PD1 complementary to oncothermia



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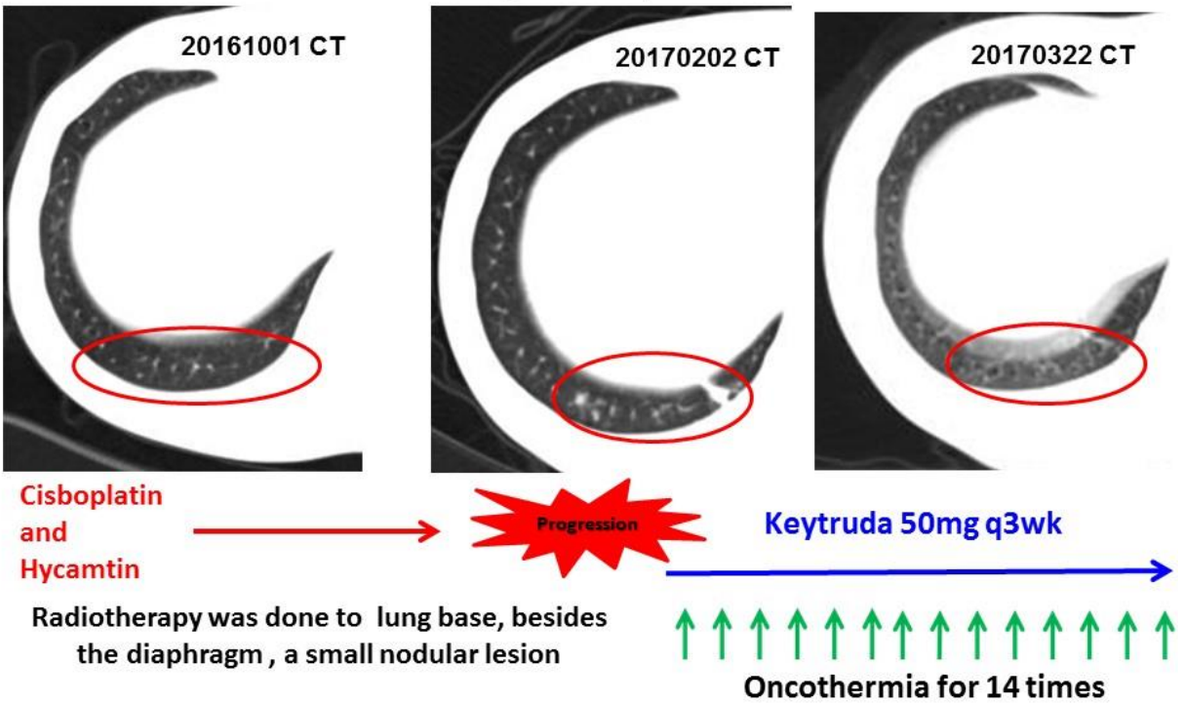
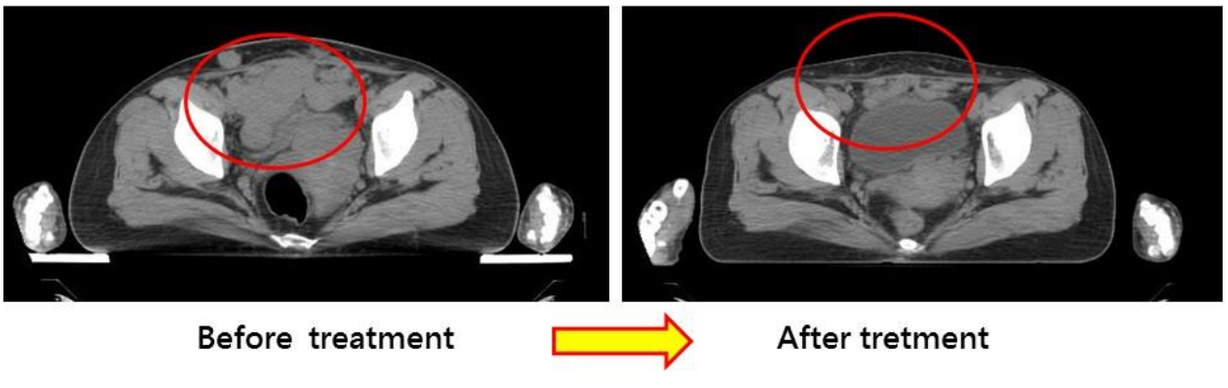


Recurrent uterine sarcoma with peritoneal seedings

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

refractory to chemotherapy and salvage with combined radiotherapy (45Gy/30fx)

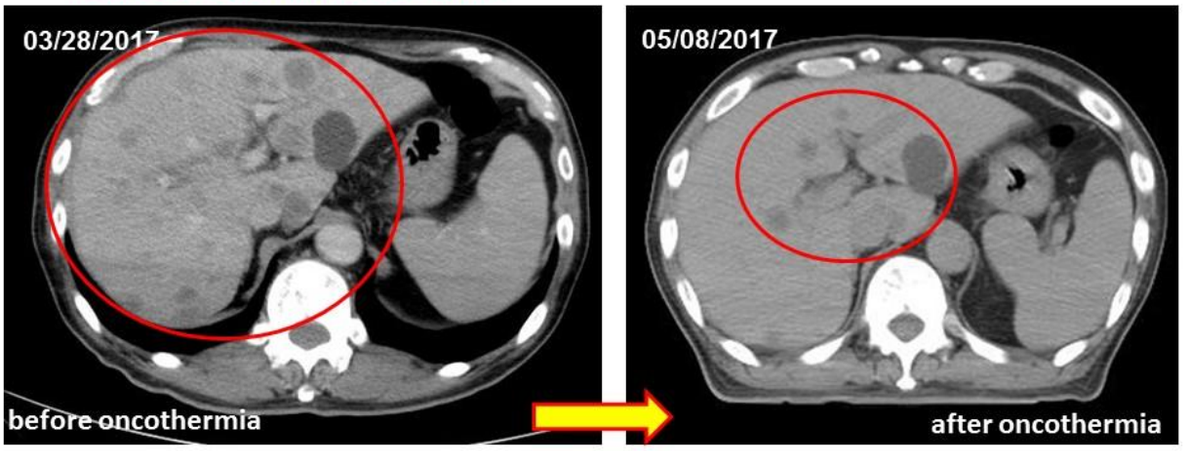


Intratumoral ipilimumab 2.5 mg, i.v. nivolumab 50 mg and complementary with oncothermia (1/week)

Hormone refractory prostate cancer, refractory to salvage

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

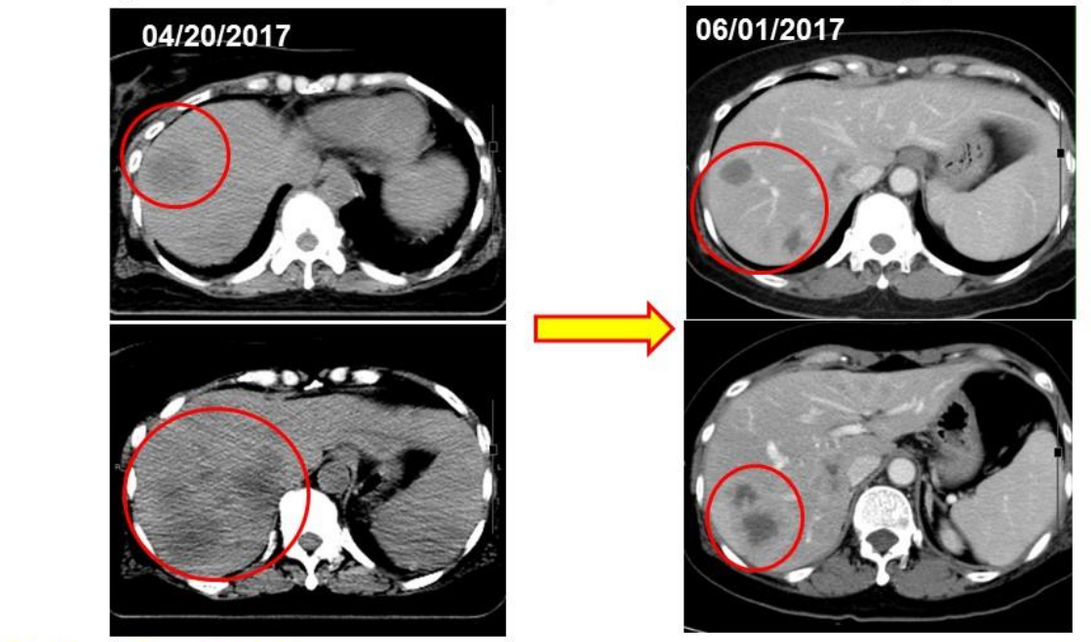
100mg Keytruda+ 100mg Doxetaxel
every 3 weeks for 4 cycles,
liver progression until oncothermia,



Salvage oncothermia 8 times, enzalutamide 160mg qd, and Keytruda 100mg q3w, good response.

Breast cancer with liver metastases

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

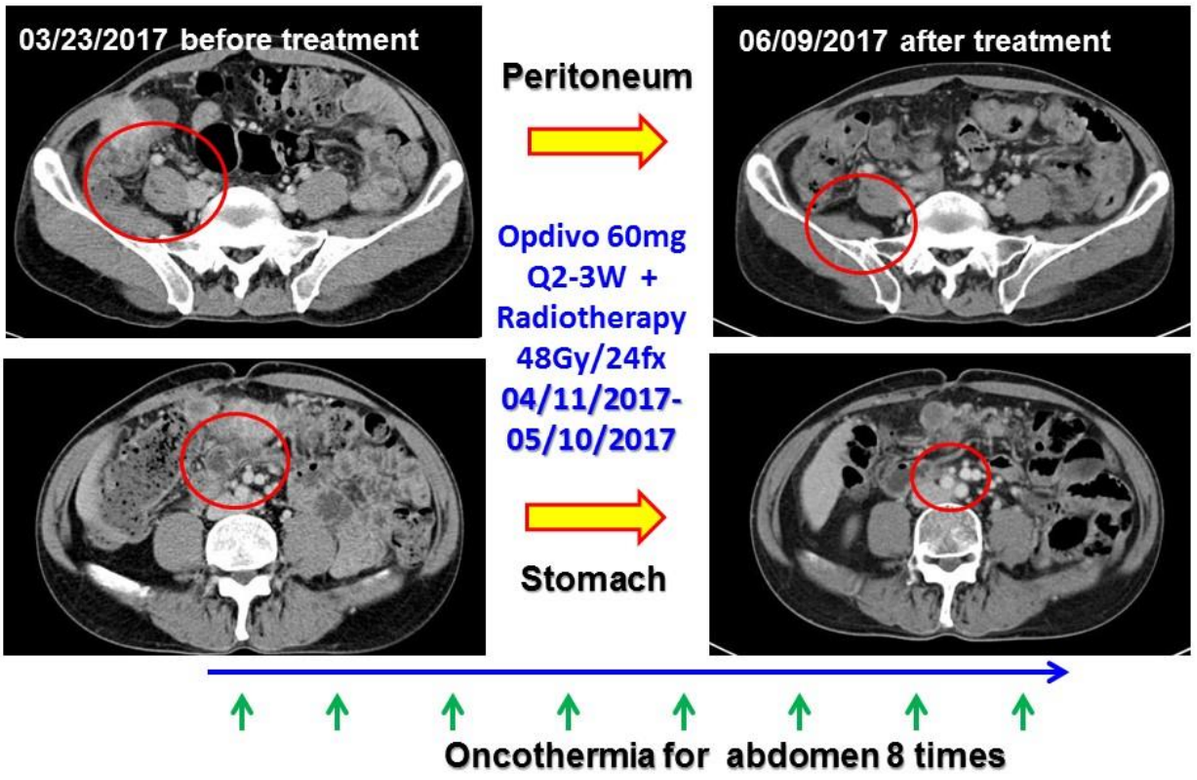


Opdivo 60mg Q2-3W
+
Cisplatin +5FU

Oncothermia for liver 6 times

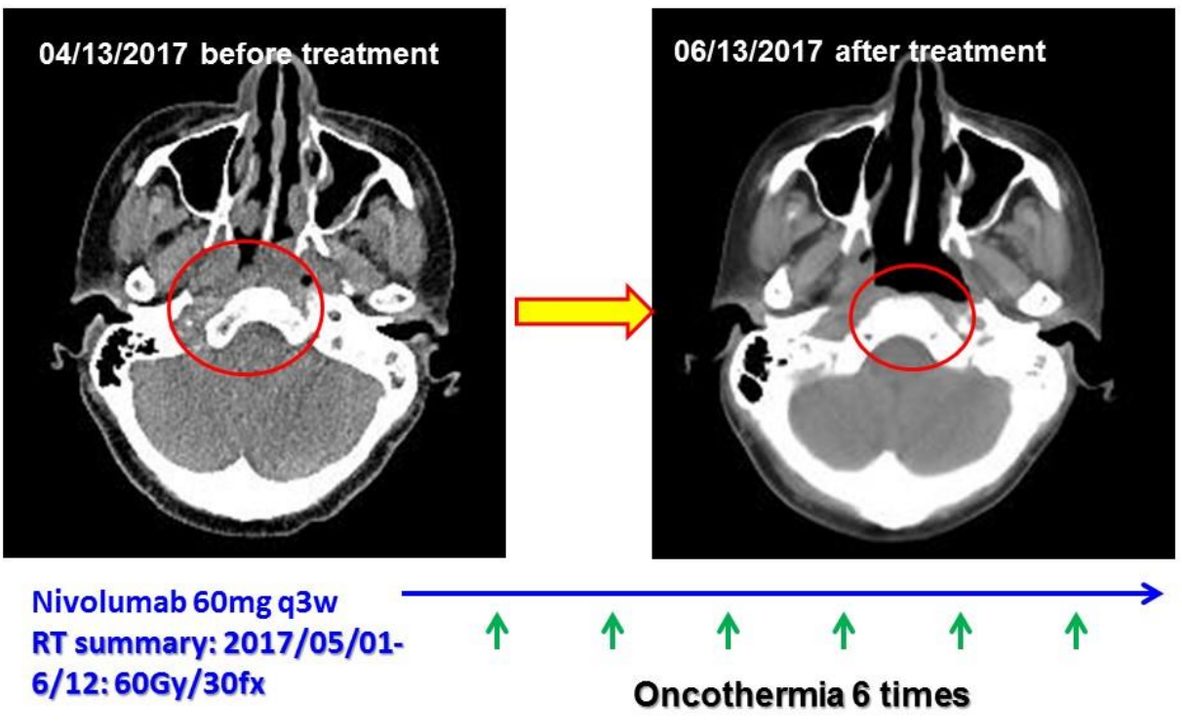
Stomach cancer with peritoneal seedings

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

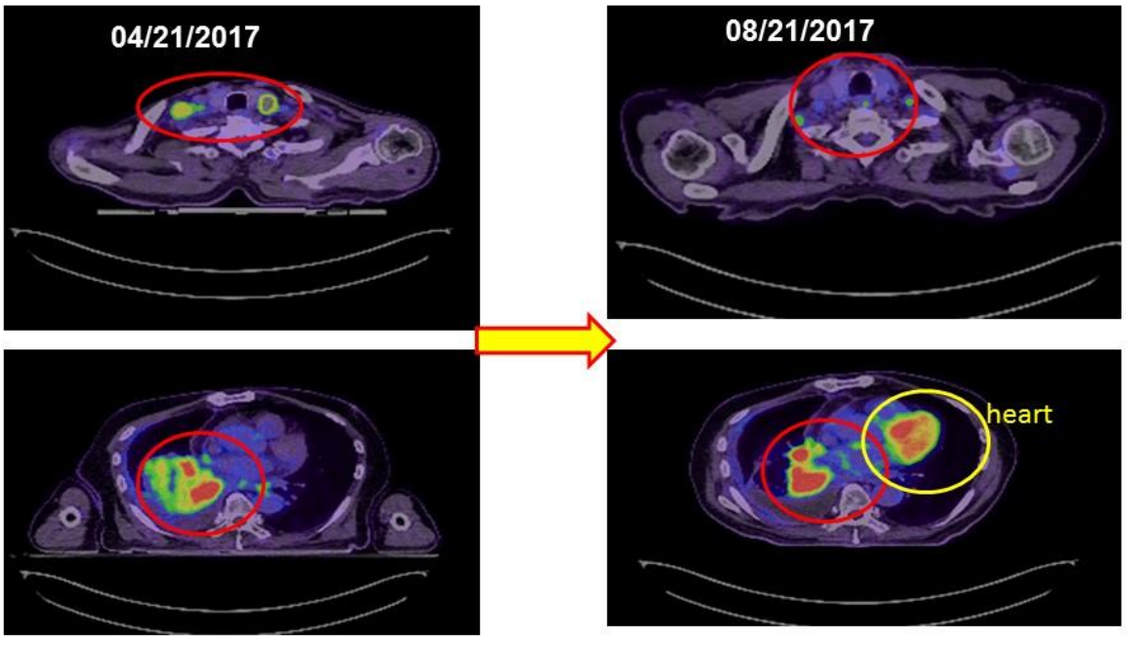


Recurrent nasopharyngeal carcinoma

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)



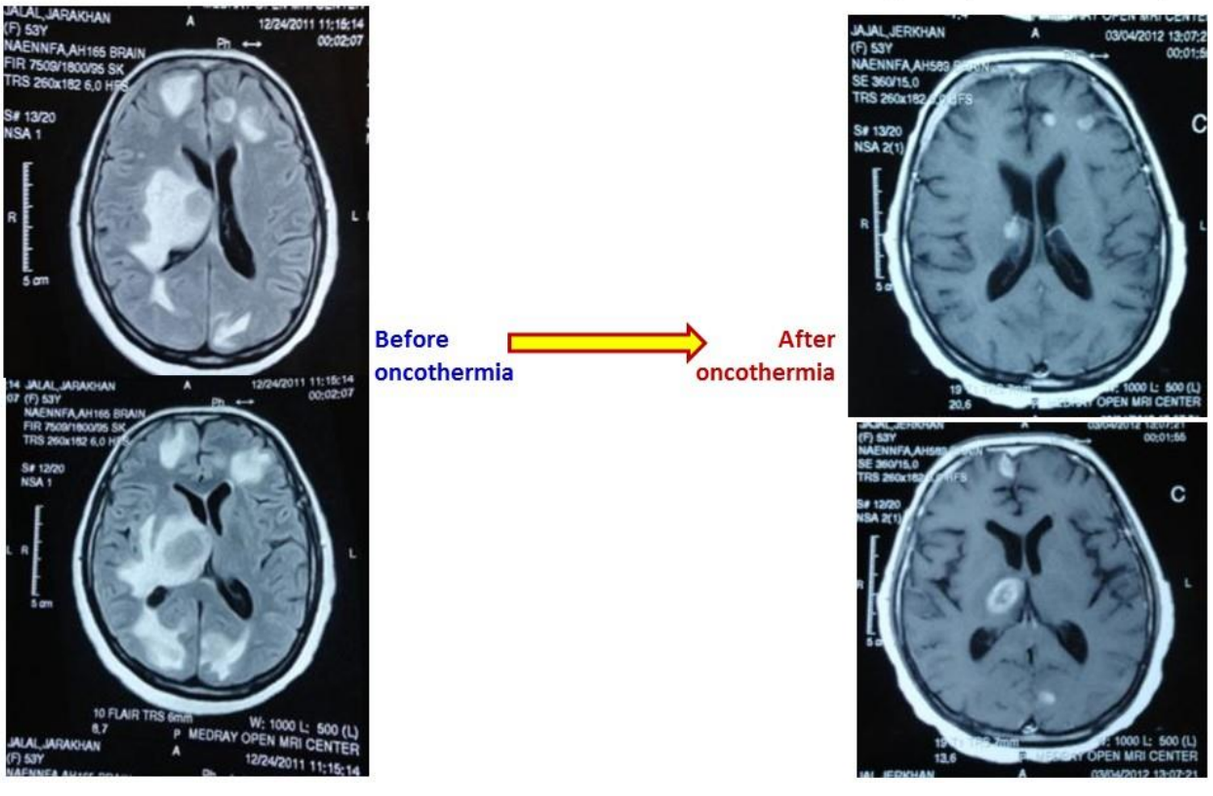
Lung adenocarcinoma failure from previous CCRT



Avastin 300mg: 2017/4/26, 200mg on 2017/5/9, 5/24, 6/6, 6/20, 7/4, 7/18, 7/31, 8/15
Nivolumab 60mg Q2W: 2017/5/9, 100mg: 5/24, 6/6, 6/20, 7/4, 7/18, 7/31, 8/15
RT to SCF and mediastinum LNs: 2017/05/08-6/6, total 44Gy/20Fx.
Oncothermia : QW (5/9~8/17, total 15 fx).

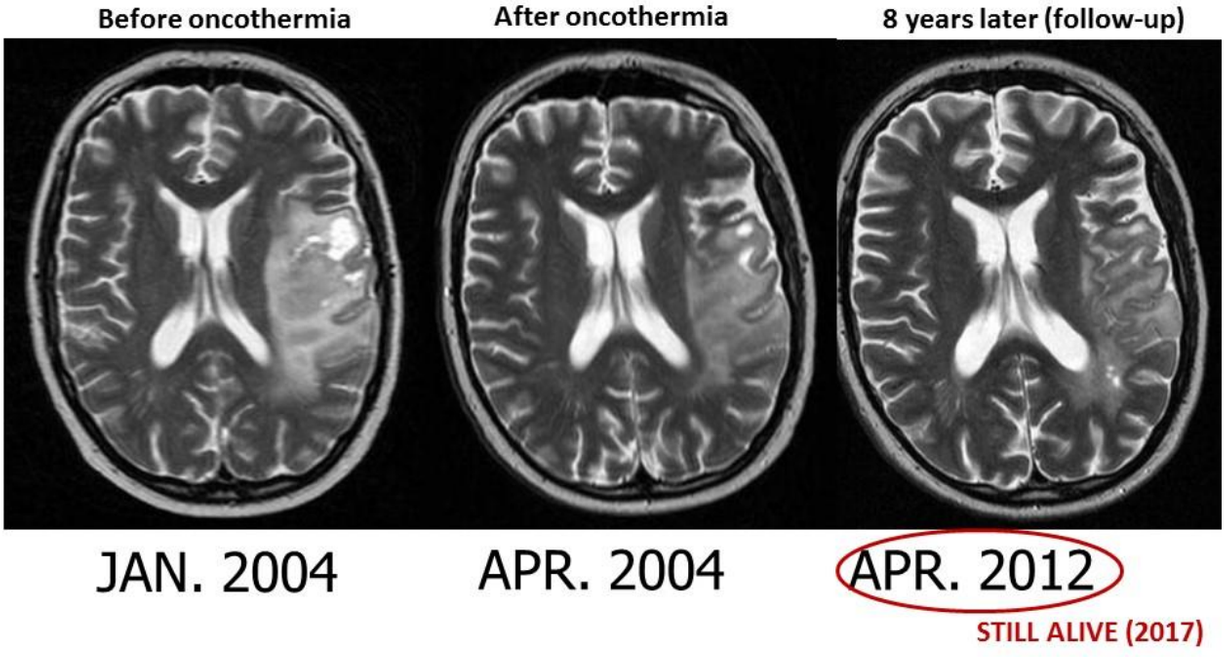
Brain metastasis from breast cancer

Investigator: Dr. Marwan Akasheh; **Institute:** Dar Alshefa' Tumors Treatment Center, Amman, Jordan, **Patient**: female 53 y.



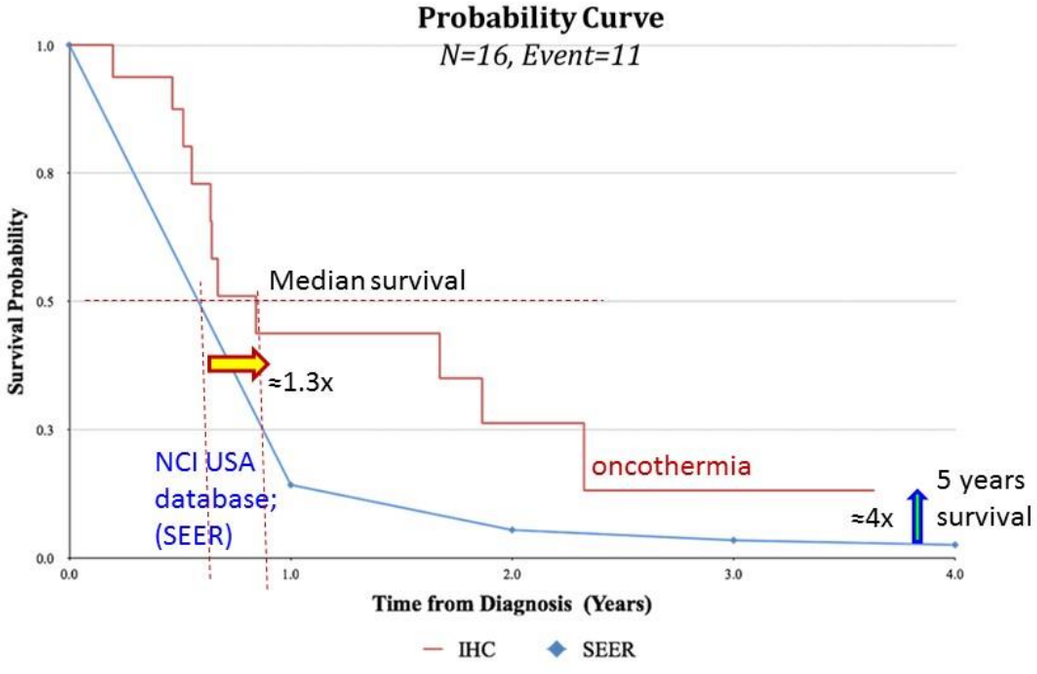
Astrocytoma, relapsed

Investigator: Prof.Dr. G. Fiorentini
Institute: Dept. of Oncology Azienda Ospedaliera Marche Nord, Pesaro, Italy
Diagnosis: relapsed anaplastic astrocytoma, GIII
Therapy: Oncothermia



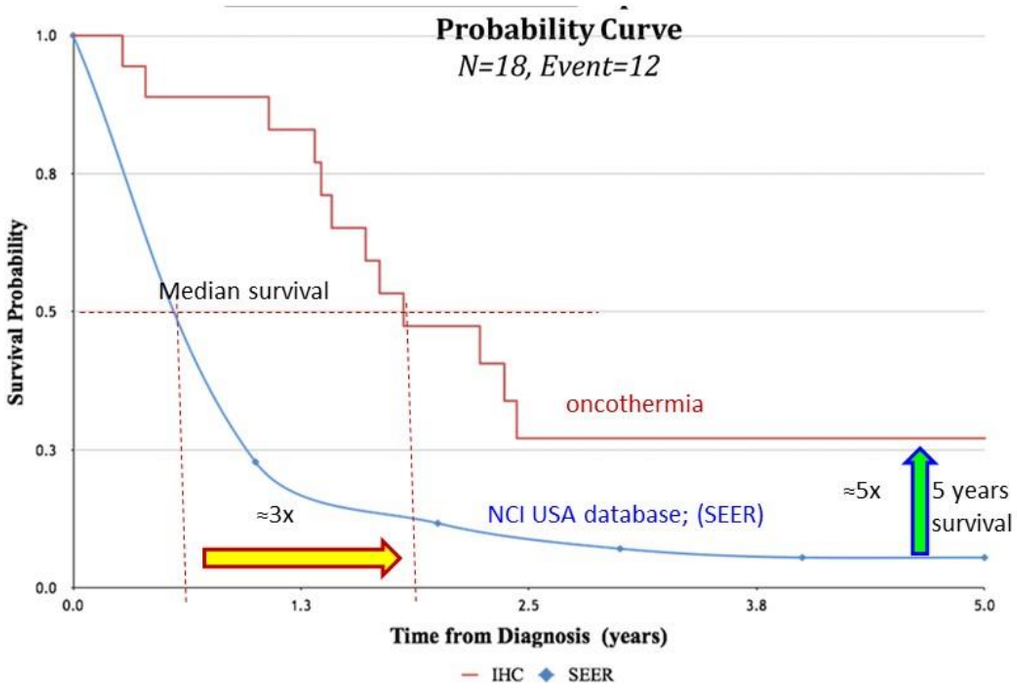
Non-resectable pancreatic adenocarcinoma

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



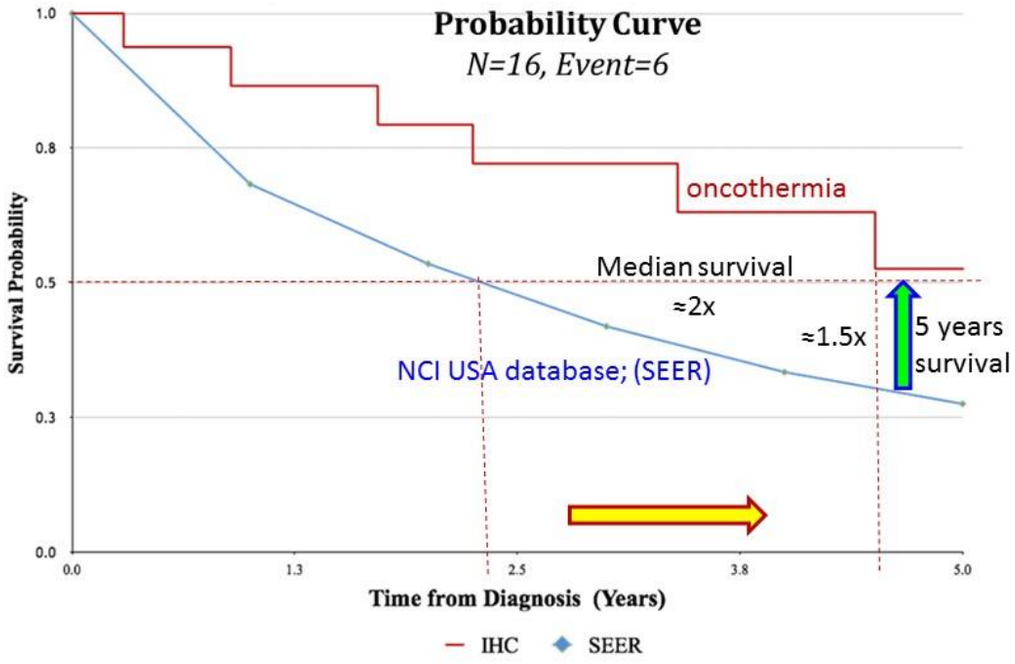
Gliobalstoma multiform

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



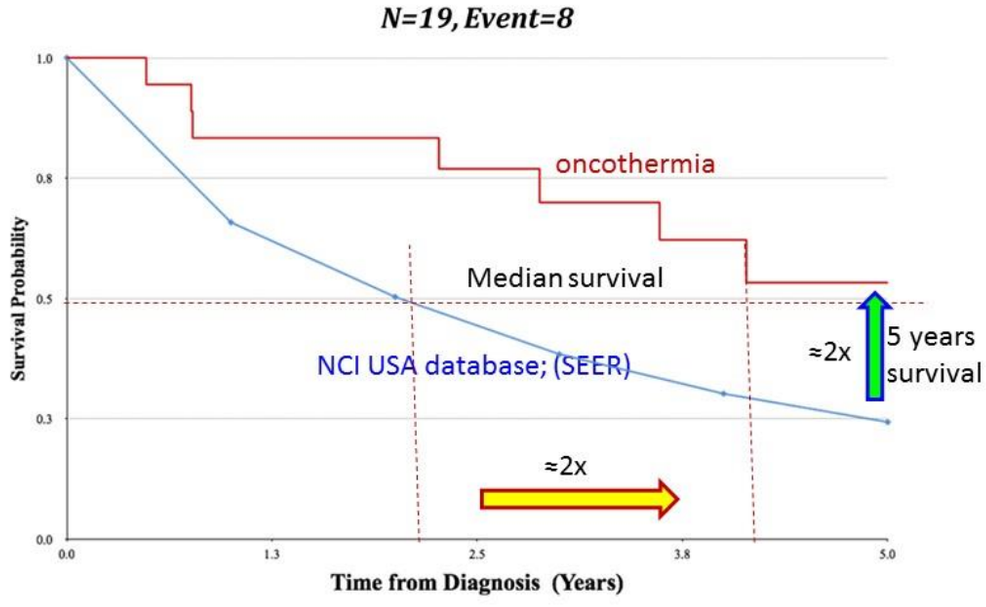
Advanced ovarian cancer

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



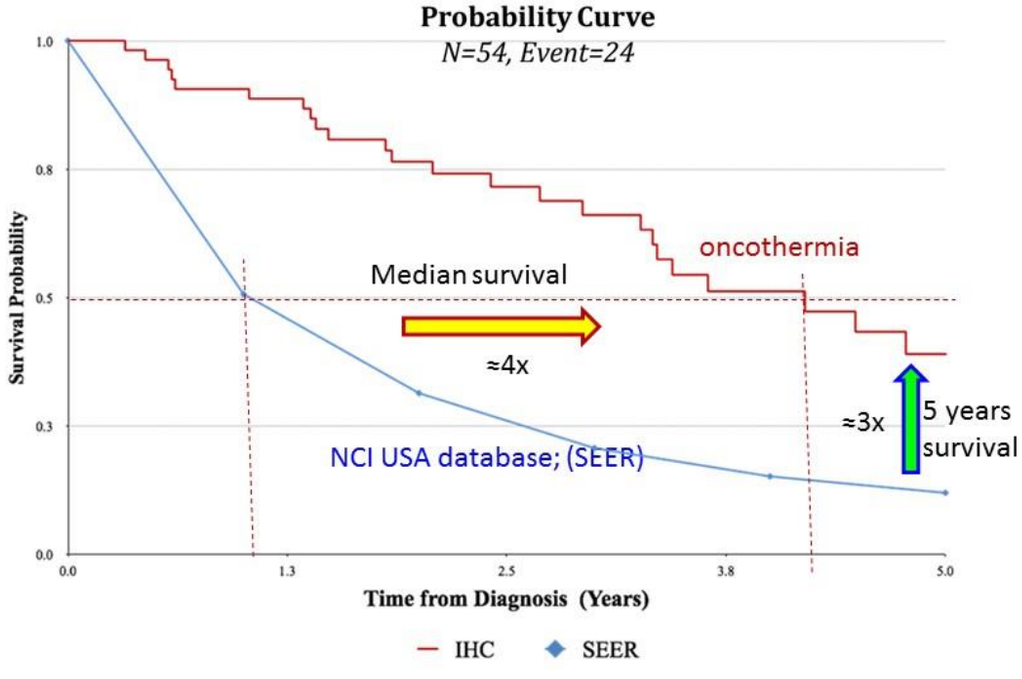
Metastatic breast cancer

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



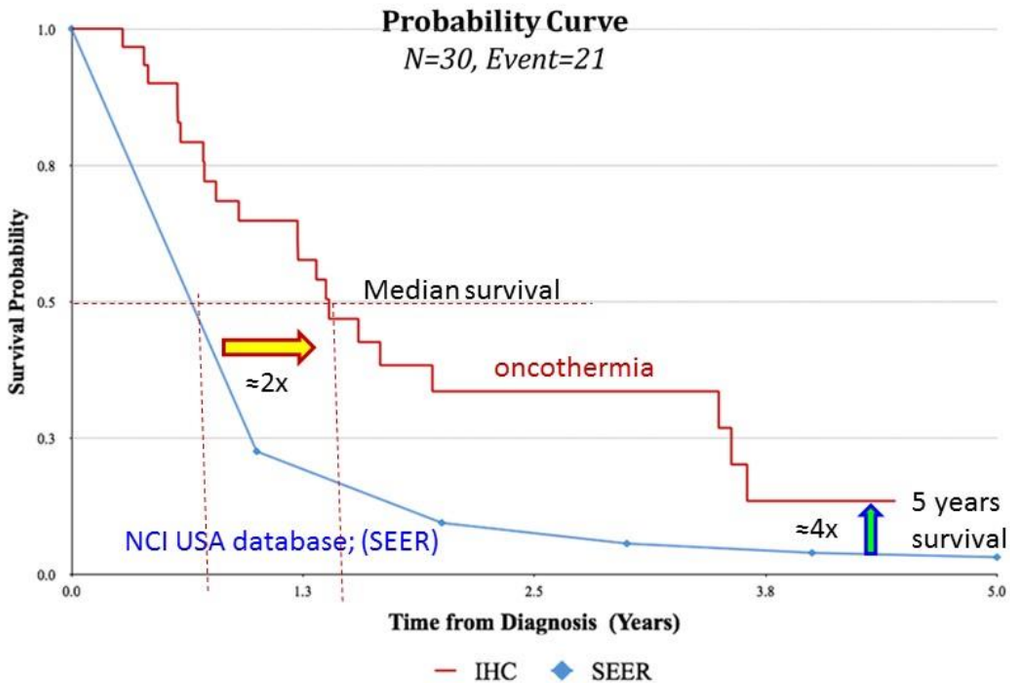
Metastatic colorectal cancer

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



Metastatic lung

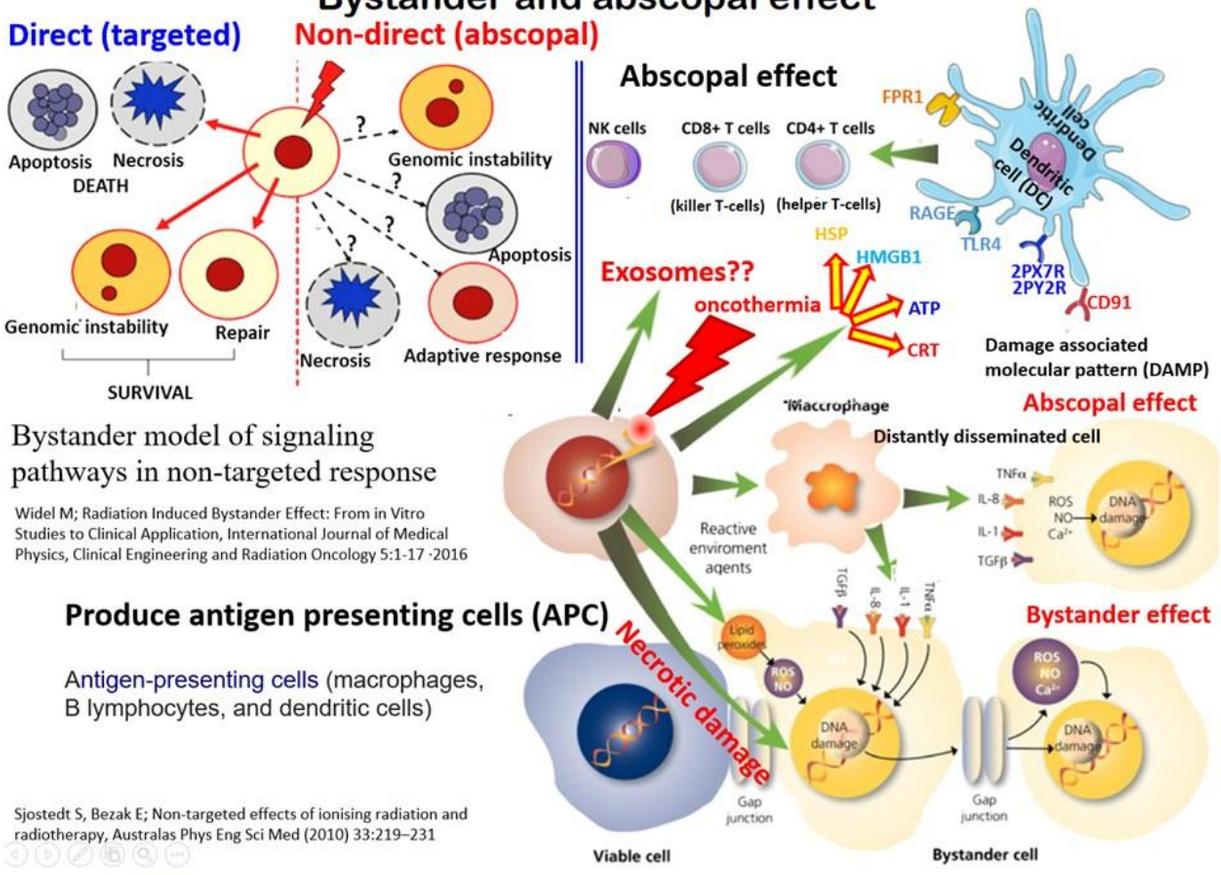
Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



Outline

- ❑ Challenges (hyperthermia at crossroads)
- ❑ Oncothermia basic principles
- ❑ Oncothermia new results
- ❑ Breakthrough perspectives
- ❑ Take-home messages

Bystander and abscopal effect



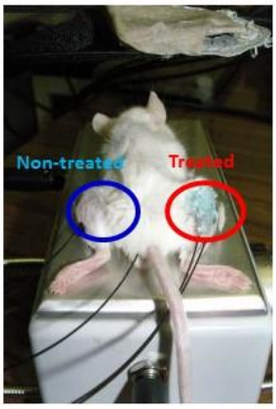
Bystander model of signaling pathways in non-targeted response

Widel M; Radiation Induced Bystander Effect: From in Vitro Studies to Clinical Application, International Journal of Medical Physics, Clinical Engineering and Radiation Oncology 5:1-17 ·2016

Produce antigen presenting cells (APC)

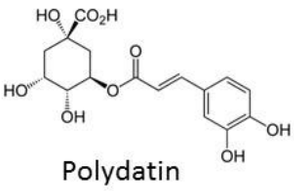
Antigen-presenting cells (macrophages, B lymphocytes, and dendritic cells)

Sjostedt S, Bezak E; Non-targeted effects of ionising radiation and radiotherapy, Australas Phys Eng Sci Med (2010) 33:219–231

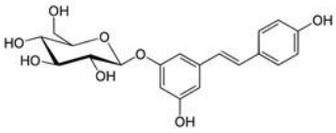


Marsdenia tenacissima (MTE, Xiao-aiping) injection before Oncothermia

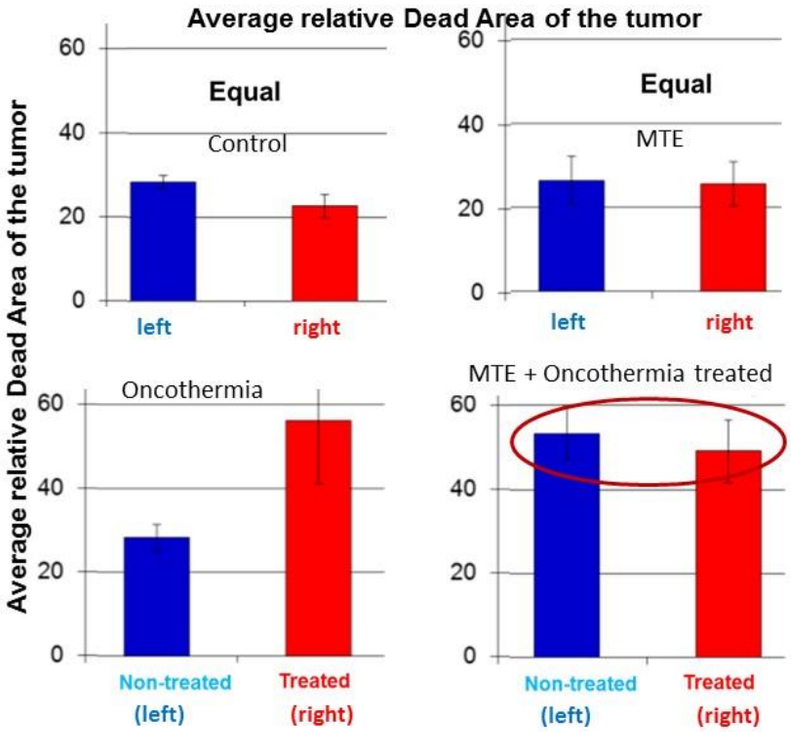
Chlorogenic-acid (11 mg/ml)



Polydatin

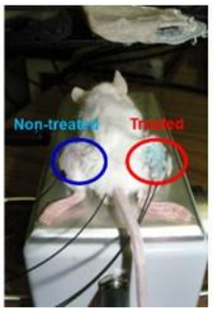


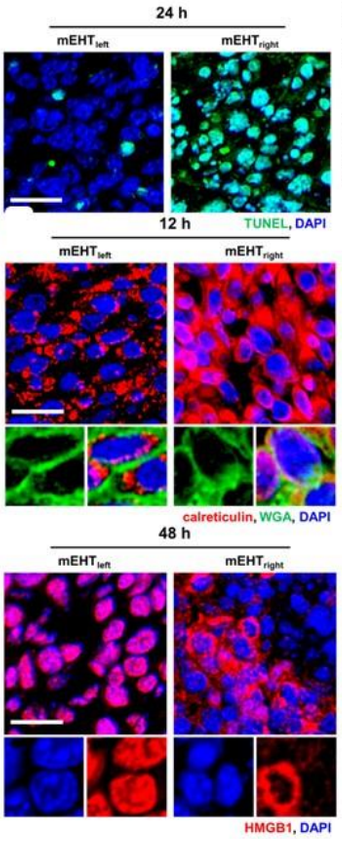
Abscopal effect by Xiao-aiping (MTE)

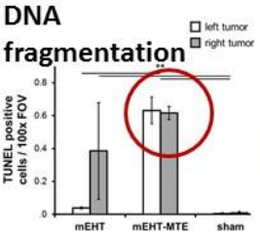


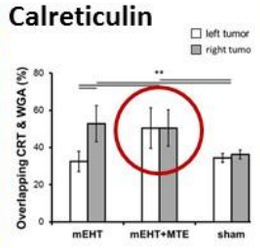
The abscopal effect is clearly proven

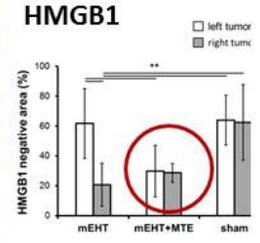
Abscopal effect by Xiao-aiping (MTE)

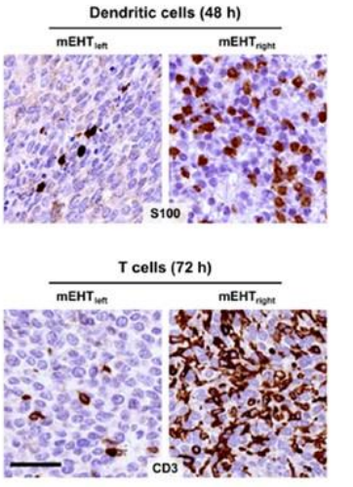


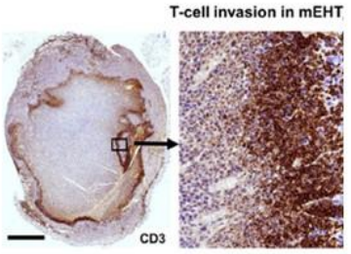








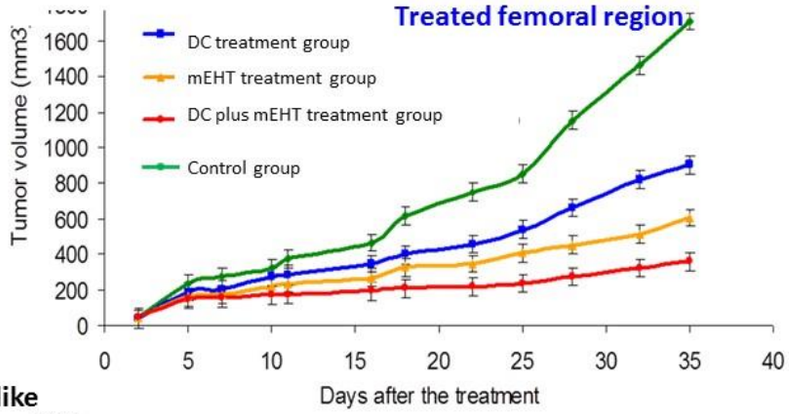




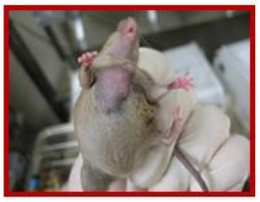
Vancsik T, et al: (2017) Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts, J. Cancer, http://www.jcancer.org/v09p0041.htm

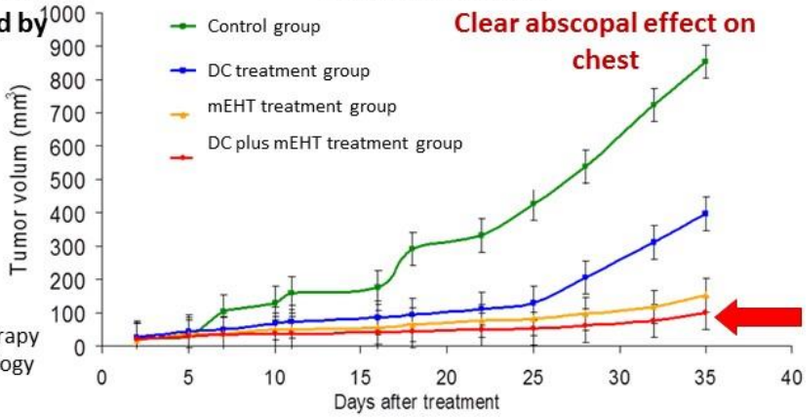
mEHT+ DC therapy combination

Tumor induced on femoral region (treated by nanothermia)



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



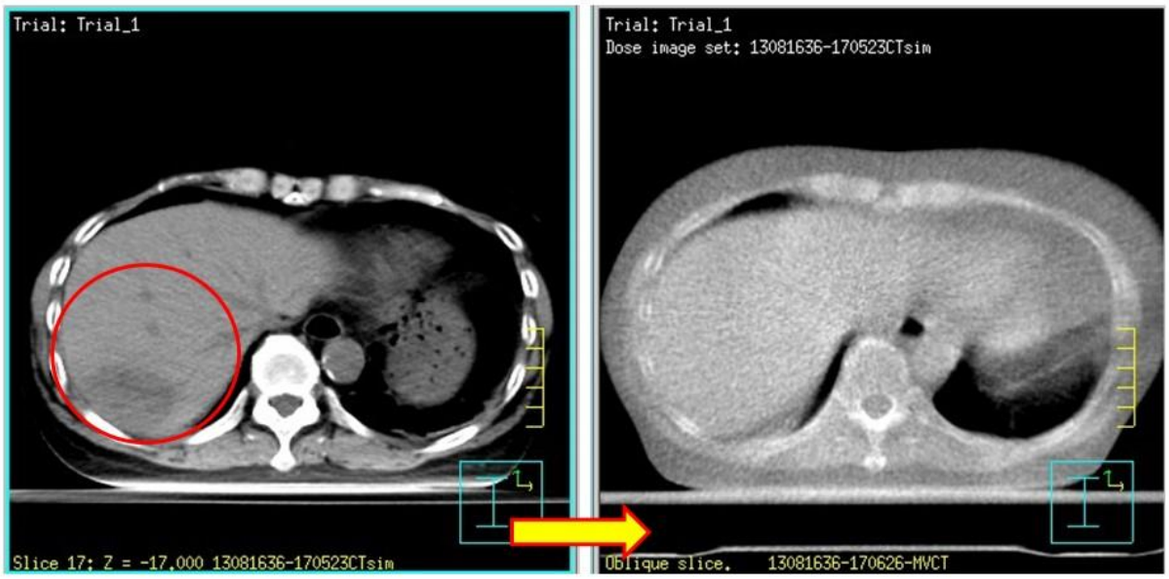


Wei Quin et.al; Modulated electro-hyperthermia enhances dendritic cell therapy through an abscopal effect in mice; Oncology Reports 32: 2373-2379, 2014

Abscopal Effect on Liver mass

Wang Y-S, Chi K-W, National Chiao Tung University, Hsinchu, Taiwan (unpublished yet)

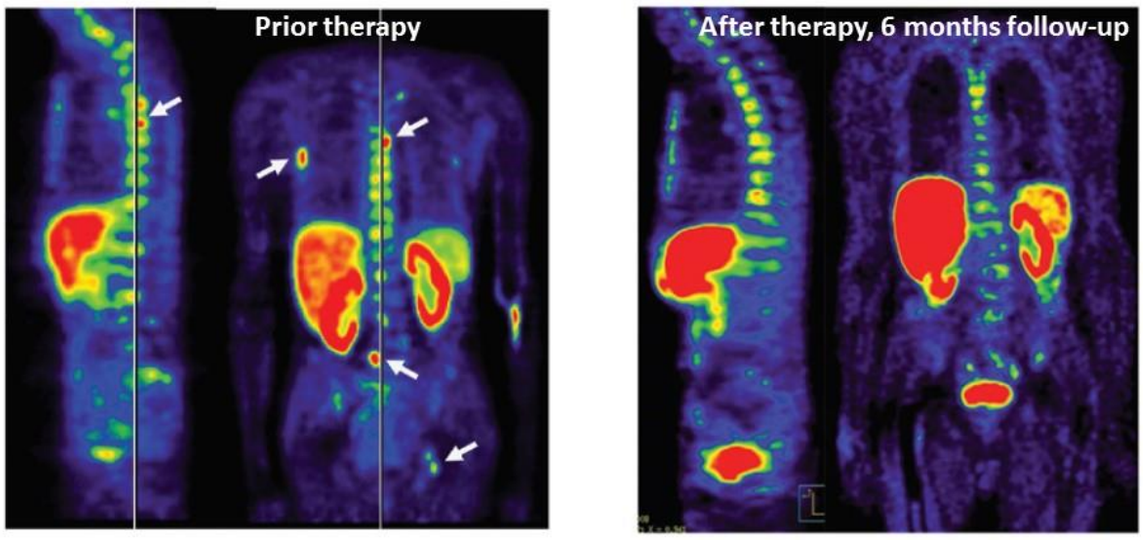
Radiation therapy (RT) for urothelial-cell carcinoma (UCC) of renal pelvis with abdomen and liver metastases
RT to abdomen mass was 40Gy complementary oncothermia 6 times
(no liver treatment was performed!)



Abscopal effect: bone metastasis of prostate cancer

Schirrmacher V, Bihari A-S, Stucker W, Sprenger T; Long-term remission of prostate cancer with extensive bone metastases upon immuno- and virotherapy: A case report; Onco. Lett. 8:2403-2406, 2014

^{18}F-choline-positron-emission-tomography/computed tomography scans.



Multiple focal tracer enhancements in the spine, 5th right rib and pelvis.

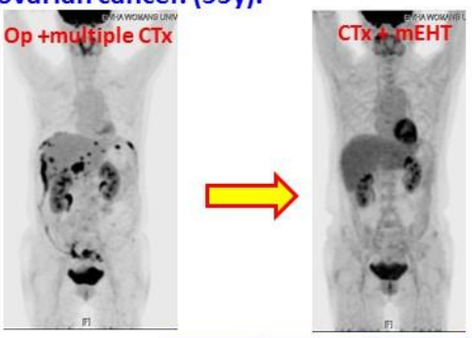
Newcastle-disease virus + mEHT + DC

Distinct regression of skeletal metastases, no more focal enhancement observable. Mild diffuse tracer enhancement in thoracic spine, representing low remaining metabolic activity.

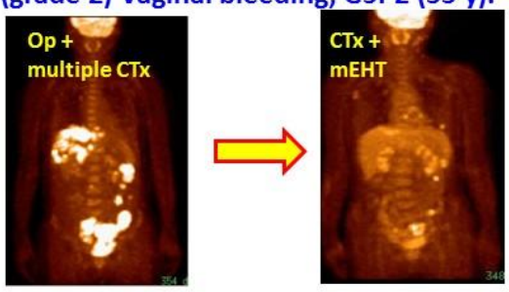
Abscopal effect

Investigator: Prof. Dr. YH Kim; Ewha Womans University Mokdong Hospital, Seoul, Korea

Recurrent refractive progressive ovarian cancer. (55y).

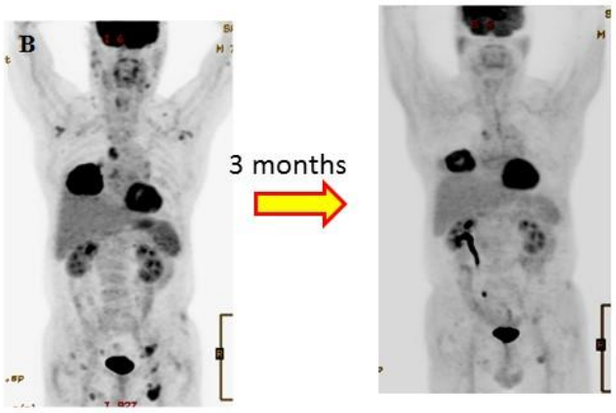


Invasive adenocarcinoma of ovary (grade 2) Vaginal bleeding; G5P2 (33 y).



Metastatic non-small-cell lung cancer (55y).

Investigator: Prof. Dr. Seong Min Yoon,
Division of Hematology-Oncology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University, Korea
Patient: SAsc, 72 y, 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 Mx, stage IIIB
Treatment: 28x1.7 Gy; support: **250 microgram Leukine (GM-CSF) and Oncothermia 6x**



Outline

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- ❑ **Breakthrough perspectives**
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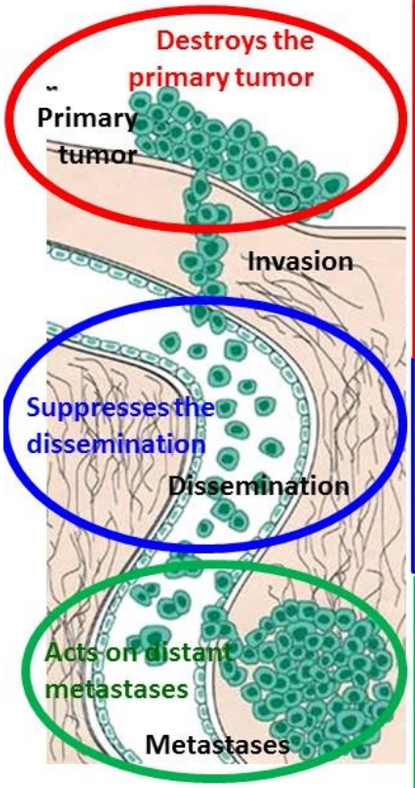
The mission accomplished

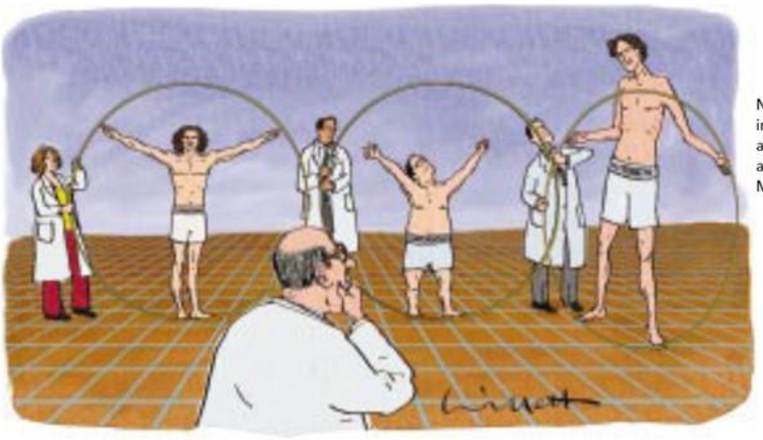


Selectively destroys the malignant cells with high metabolic rate
Szasz A, et al. (2003) Magneto- and electro-biology 22(2):103–115
Induces massive apoptosis (produces apoptotic bodies)
Meggyeshazi N, et al. (2014) Strahlenther Onkol 190:815-822
Apoptotic signal starts from the cell-membrane
Andocs G, et al. (2015) Biology and Medicine 7(4):1-9
Expression of: mHSP70, mHSP90, Trail-R2, CRT, Cyt-C, HMGB1
Andocs G, et al. (2014) Cell Stress and Chaperones 20(1):37-46
Regulates different genes than the same temperature heating
Andocs G, et al. (2016) Cell Death Discovery (Nature Publishing Group), 2, 16039
Produces immunogenic cell-death (ICD)
Andocs G, et al. (2014) Cell Stress and Chaperones 20(1):37-46
Forms APC with ICD process
Meggyeshazi N, et al. (2013) Hindawi, Conference Papers in Medicine, Volume 2013, Article ID 187835

Reestablishes the cellular connections (E-cadherin)
Yang K-L, et al. (2016) Oncotarget, oi: 10.18632/oncotarget.11444
Forms bonding connections (β-catenin)
Szasz A (2013) Thermal Med 29(1):1-23
The primary tumor is enveloped by lymphocytes
Szasz A, et al. (2013) A chapter in book Ed: Huilgol N, ISBN 980-953-307-019-8, InTech,
Activates the neutrophils in the envelop
Szasz A, et al. (2010) Springer Science, Heidelberg

Creates abscopal effect
Qin W, et al. (2014) Oncol Rep 32(6):2373-2379
The rechallenge could not be forced
Yuk-Wah Tsang, et al. (2015) BMC Cancer 15:708
Immune (and/or small-vehicles) actions
Kleef R, et al. (2012) Case Rep Oncol 5:212-215; SchrrmacherV, et.al. (2015) Immunotherapy 7: 855–860; Volker S, et al. (2014) Oncology Letters 8:2403-2406
Tumor-specific immune-reactions (vaccination)
Patent (EU) http://www.google.com/patents/EP2703001A1?cl=en,
Patent (USA) http://www.freepatentsonline.com/20150217099.pdf

The challenge of the conventional thinking



Nahin RI, Starus SE; Research into complementary and alternative medicine: problems and potential, British Journal of Medicine 322:161-164 (2001)

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

Thank you very much!