Modulated electro-hyperthermia, (mEHT)
From LAB to clinic

Oliver Szasz, PhD [1*,2], Andras Szasz, PhD[2]
(1) Oncotherm GmbH, Troisdorf, Germany, SzaszOliver@oncotherm .de
(2) Department of Biotechnics, Faculty of Engineering, St. István University, Budaörs, Hungary *biotech@gek.szie.hu

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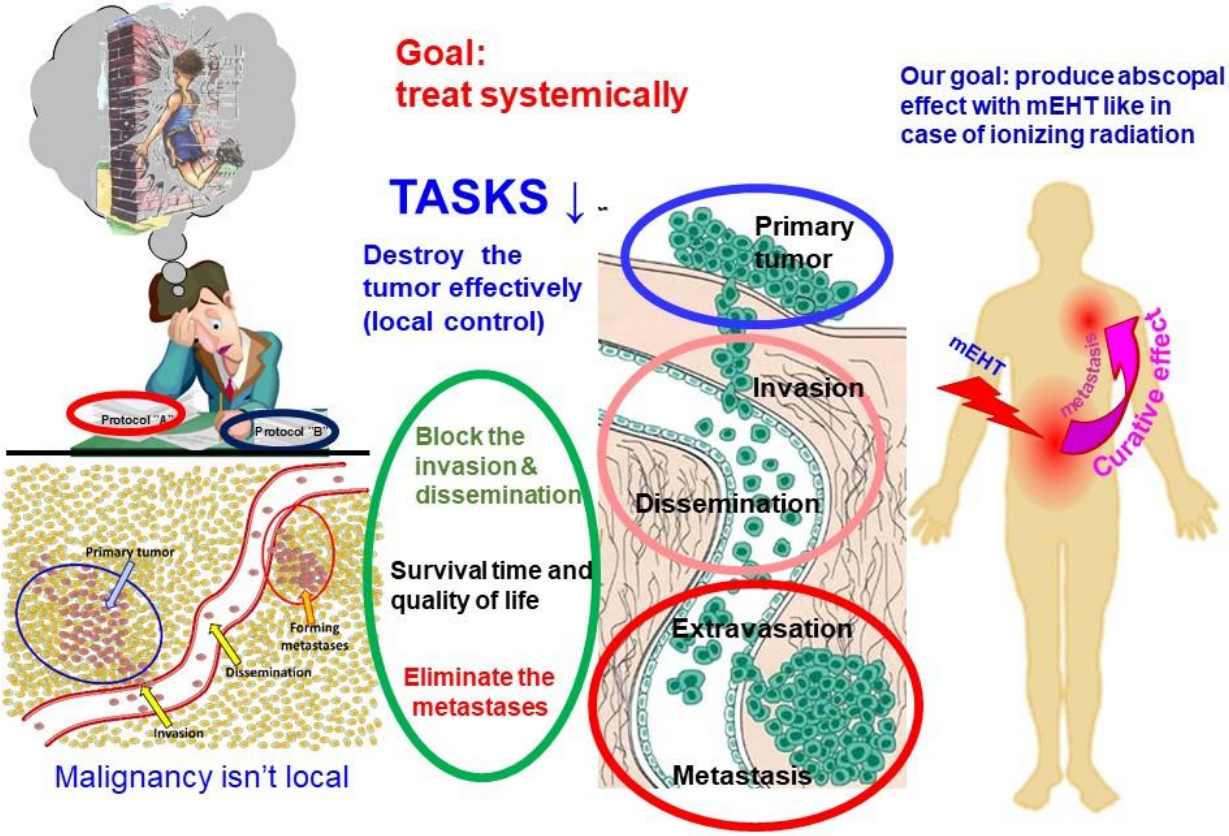
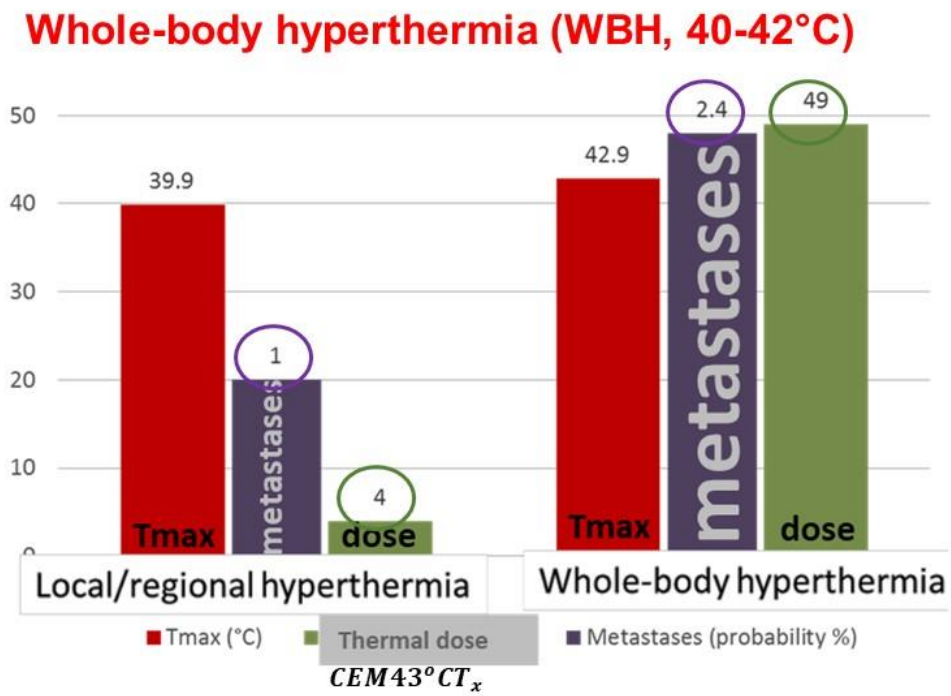
Outline

- ❑ **The challenge**
- ❑ **The methods**
- ❑ **Experimental results**
- ❑ **Clinical results**
- ❑ **Conclusions**

Challenge in oncology – malignancy is systemic



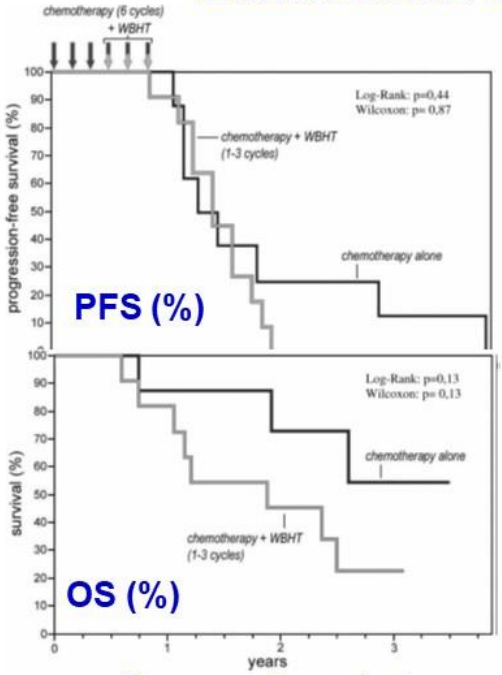
Is the task to simply heat up the tumor?



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. 34(5):1087-96., 1996

Challenges with whole-body hyperthermia (40-42°C)

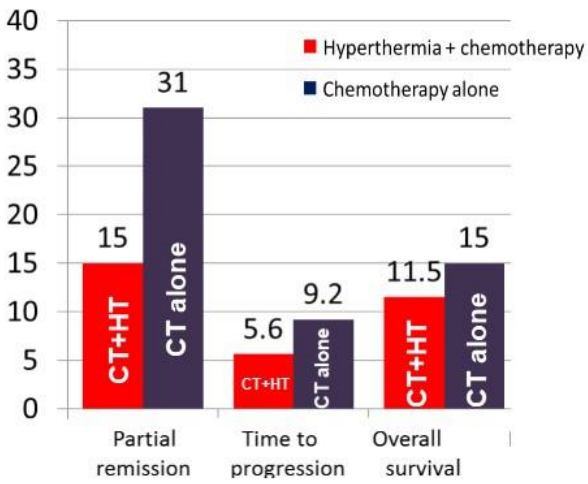
metastatic colorectal cancer



Decreases the survival

Hildebrandt B, , et al. 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

malignant pleural mesothelioma



Decreases the effect of chemotherapy

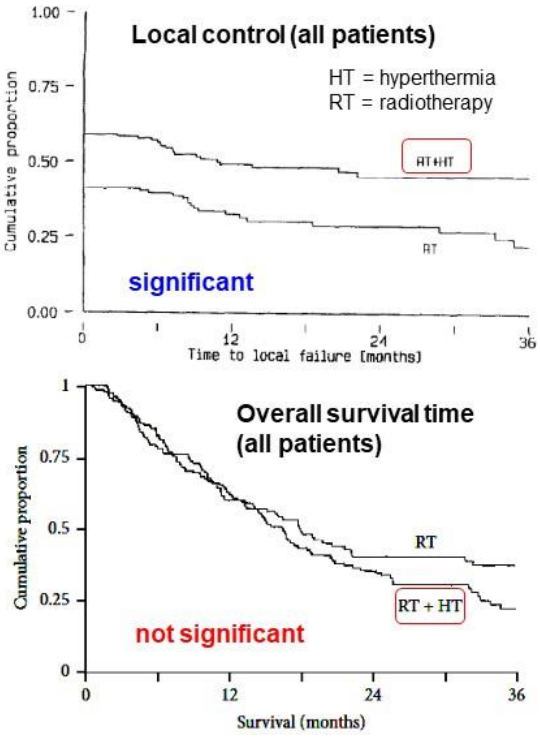
Bakhshandeh A, Wiedemann G, Zabel P, et al. Randomized trial with ICE (ifosfamide, carboplatin, etoposide) plus whole body hyperthermia versus ICE chemotherapy for malignant pleural mesothelioma. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). 22:14S, 7288. (Supplement), 2004:

Clinical challenge: Local control ↔ survival time

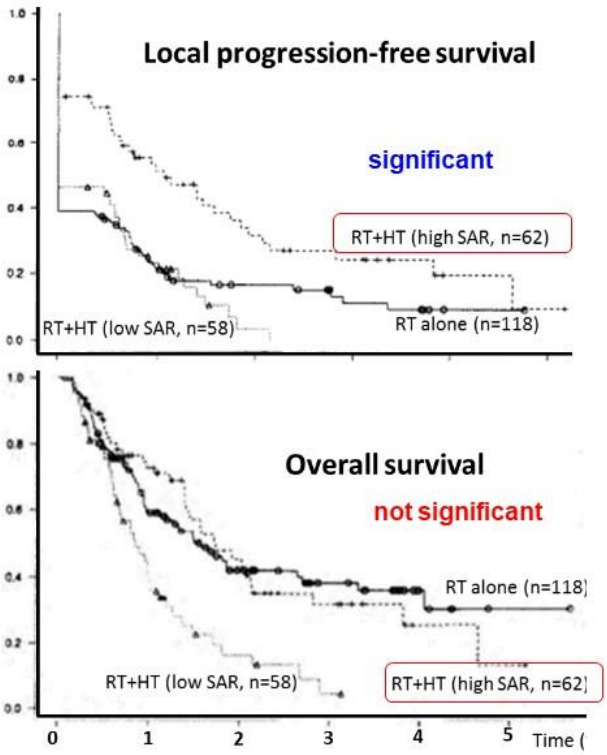
Breast studies

good local control ⟷ **no significant survival**

C. C.Vernon, et al., *Int. J. Rad. Onc. Biol. Phys*, 35:731–744, 1996



Sherar, M., et al. Int. J. Rad. Onc. Biol. Phys., 39, 371-380; 1997



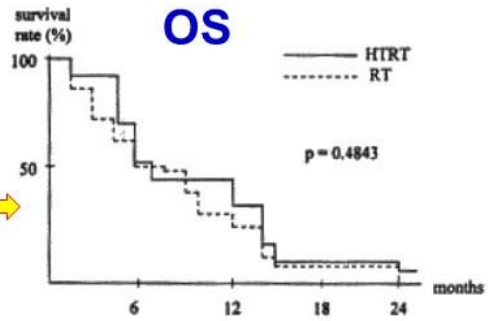
Non-small-cell lung cancer (NSCLC) RR ↔ OS

RR Initial Response Rate by Treatment Methods in 32 Patients

	HTRT (n=14)	RT (n=18)	P-value
Complete response	0	2	
Partial response	12	8	
No response	2	8	
Overall response rate	85.7%	55.6%	0.0424

HTRT : Thermoradiotherapy, RT : Radiotherapy

OS



. Overall survival rate by treatment methods.

Kay CS, Choi IB, Jang JY, Choi BO, Kim A, Shinn KS. (1996) Thermoradiotherapy in the Treatment of Locally advanced Nonsmall Cell Lung Cancer, J.Korean Soc. Ther. Radiol. Oncol. 14:115-122

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	

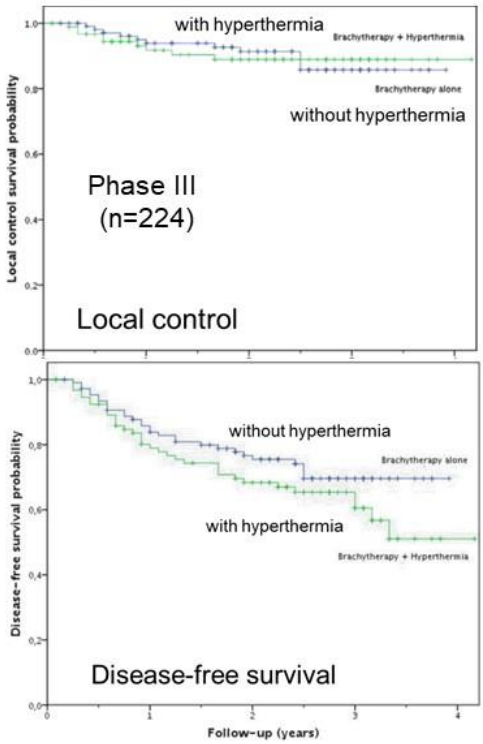
[a] Patients in whom the interval between locoregional disease progression and distant metastasis was less than or equal to 1 month

Distant metastases are induced by conventional hyperthermia

Clinical challenge: Local control ↔ survival time

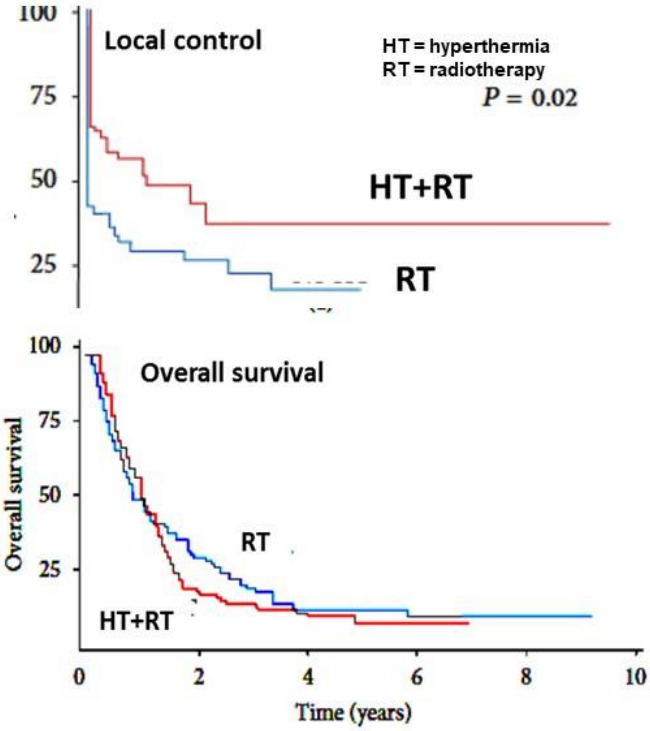
Cervix uteri (locally advanced cancer)

Zolciak-Siwinska A, et al; (2013) HDR brachytherapy combined with interstitial hyperthermia in locally advanced cervical cancer patients initially treated with concomitant radiochemotherapy – a phase III study; Radiotherapy and Oncology 109:194–199



Superficial tumors study (RT+HT)

Jones EL, et al. Randomized trial of hyperthermia and radiation for superficial tumors; J Clin Oncol. 2005; 23:3079-85



Challenge of dose of hyperthermia

$CEM43^oCT_x$ Calibrated in vitro

Sapareto and Dewey,CEM43, dose model (Sapareto SA, Dewey WC; (1984) THERMAL DOSE DETERMINATION IN CANCER THERAPYInt.J.Rad. Oncol. Biol. Phys. 10:787-800)

Unit: ^oC

$$CEM43^oCT_x = \sum_{sessions} \int_0^{t.time} R^{(43^oC - T_x)} dt$$

Unit: ??

Fits to the clinical data

Francena M, et al: Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur. J. Cancer, 45:1969-1978 (2009)

$$TRISE = \frac{1}{sessions} \sum_{sessions} \int_0^{t.time} \frac{(T_{50} - 37^oC)}{treat.time} dt$$

corresponding principle

$$SAR(t) = c\left(\frac{dT}{dt}\right)$$

Rough average (unprecise, incorrect)

Actual absorption (correct approximation)

The correct dose

$$Absorbed\ energy = \sum_{sessions} \int_0^{duration} (SAR(t))dt$$

measured in Gy (J/kg)

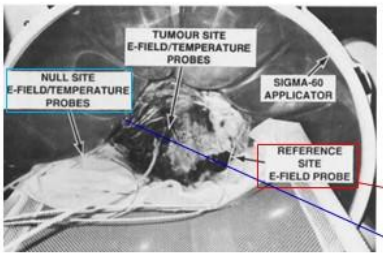
(like in ionizing radiation)

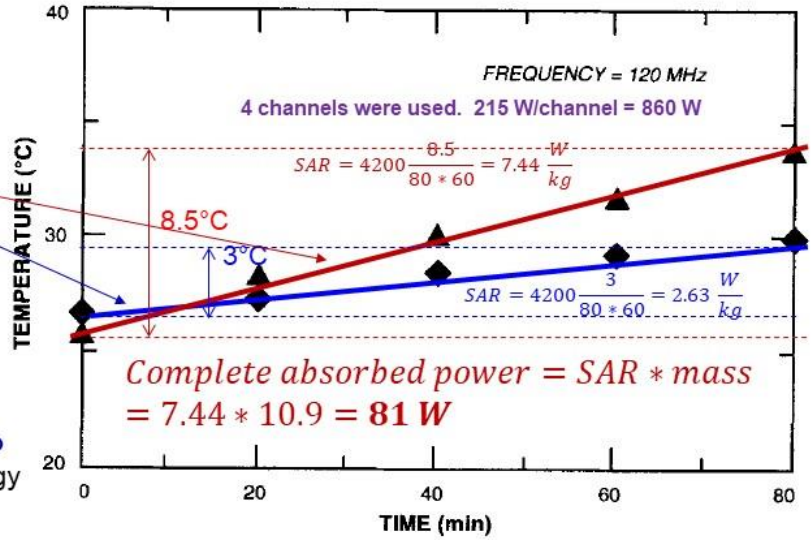
Technical requirement:
high efficacy of energy absorption

Serious technical challenge

Temperature measurement in a phantom

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





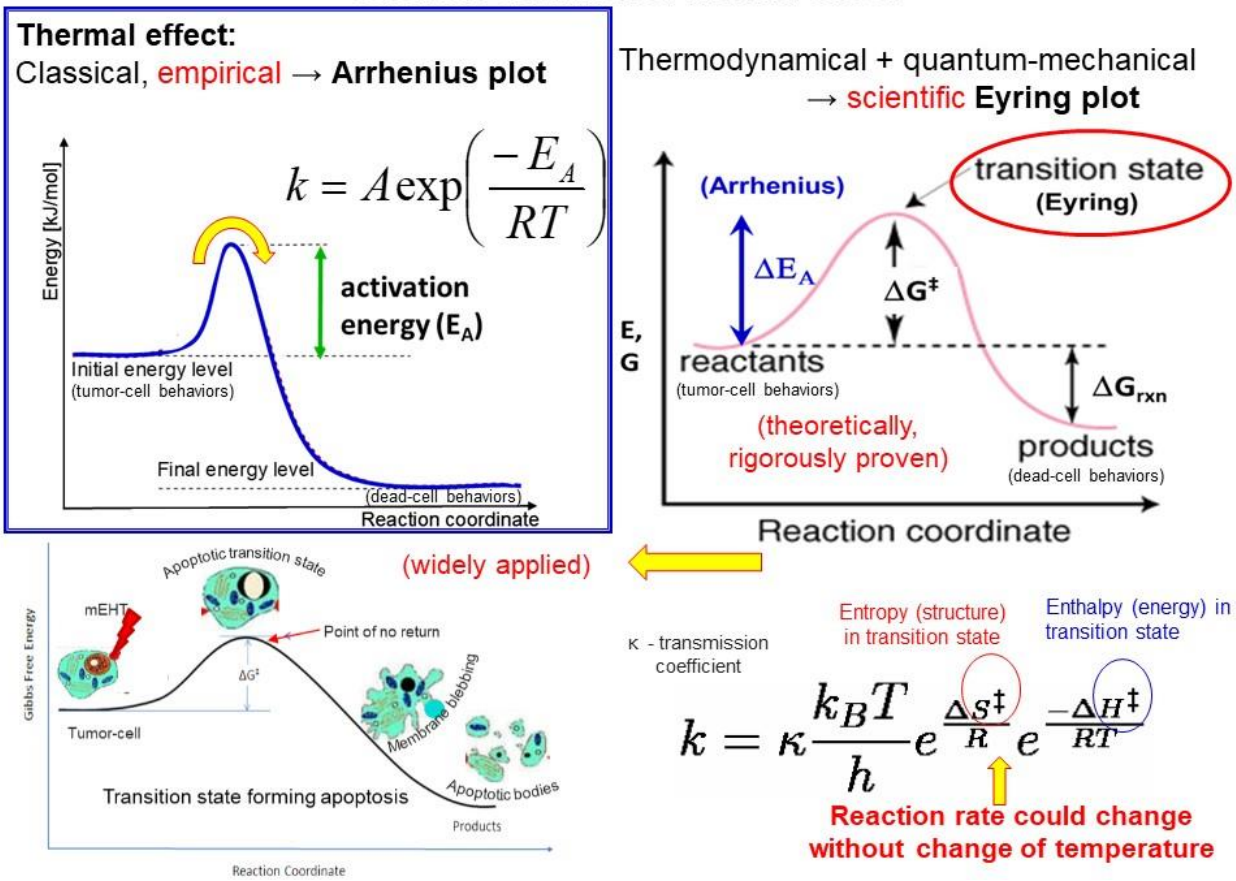
Efficacy of heating<10%

Here the measurement of the **temperature** is the **only way to approximate** the absorbed energy

Consequences

1. The energy can not be used like it is in the case of ionizing radiation
2. The **efficacy** of the energy-absorption must be drastically increased to use the absorbed energy as dose

Scientific definition of thermal effect



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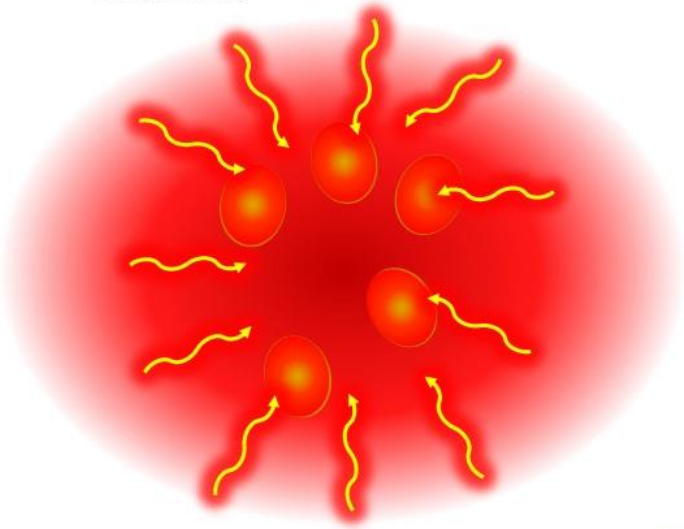
Heterogeneous vs. homogeneous

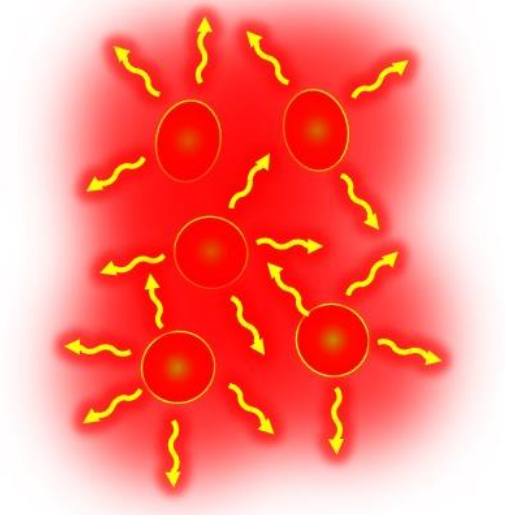
Conventional homogenic heating (radiation + convection + conduction)



The tumor is rather heterogenic, only small sizes with invasive heating could be heated approximately homogeneously

Selective, heterogenous heating (targeted molecules of selected cells)

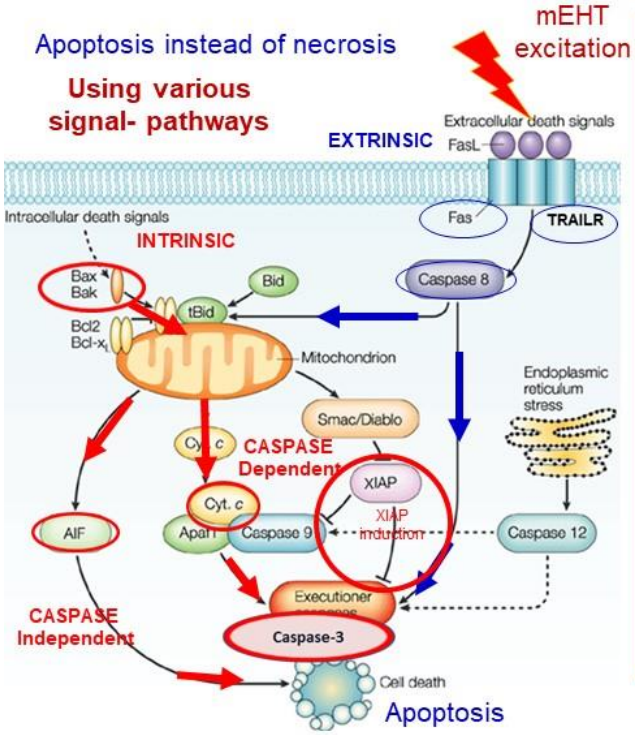
mEHT

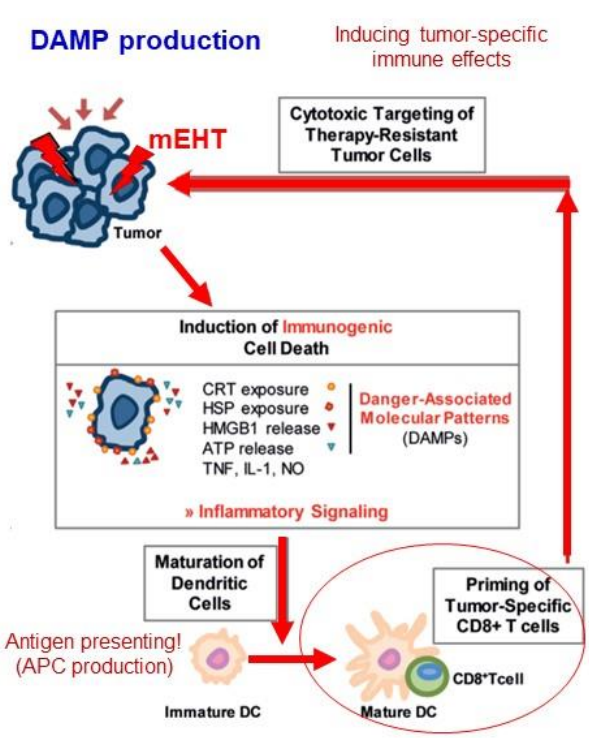


The tumor-cells have definite differences in their bioelectromagnetical/biophysical properties allowing their selected heating

High efficacy, possibility to use the Gy as dose

Abscopal: apoptosis and immunogenic cell-death





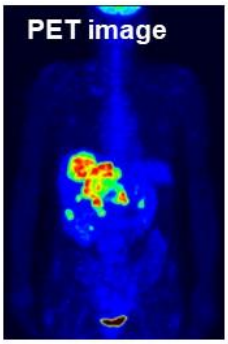
Vila M, Przedborski S; Neurological diseases: Targeting programmed cell death in neurodegenerative diseases, Nature Reviews Neuroscience 4:365–375 (2003)

Derer A, et al. Radio-immunotherapy-induced immunogenic cancer cells as basis for induction of systemic anti-tumor immune responses – pre-clinical evidence and ongoing clinical applications. Front. Immunol. 6:505, (2015)

Bioelectrodynamical selection

Oncological hyperthermia is a method to destroy malignant cells by heat-inducing absorbed energy

Select the malignant cells



Malignant tissue has much higher glucose influx and higher metabolic rate than healthy tissue

⇩

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

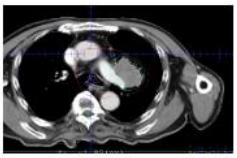
⇩

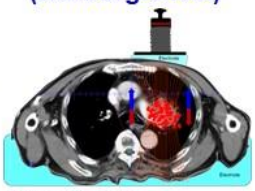
High ionic concentration

⇩

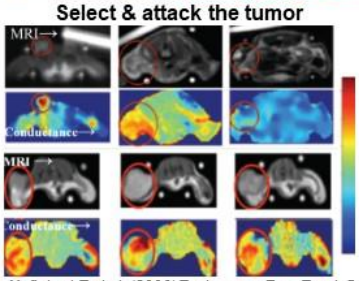
High electrical conductivity

(Warburg-effect)

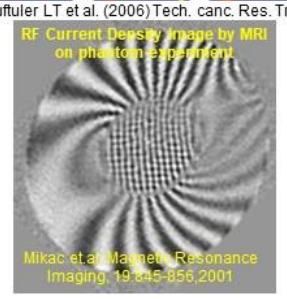




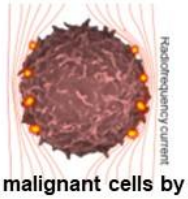
Select & attack the tumor



Muftuler LT et al. (2006) Tech. canc. Res. Treat. 5:381-387

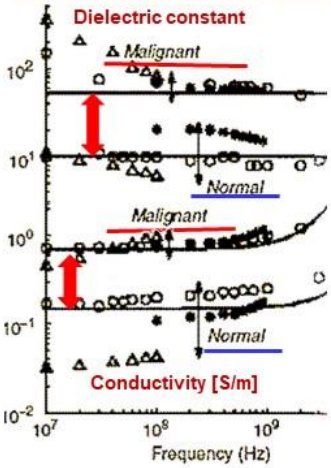


(Szentgyorgyi-effect)



Select malignant cells by autonomy

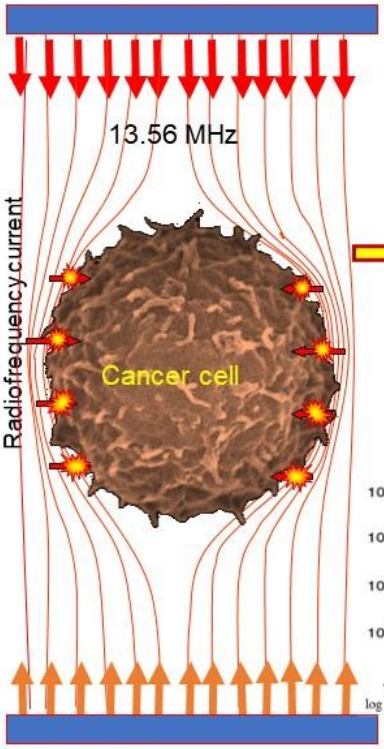
Selection by connection differences



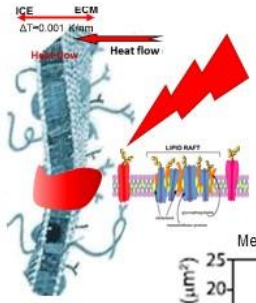
Chaudharyet SS. et al, Ind.J.f Biochem. Biophys., 21:76-79, 1984.

Bioelectrodynamical energy absorption

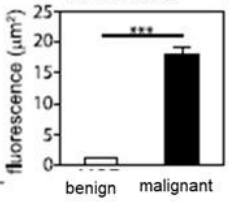
Oncological hyperthermia is a method to destroy malignant cells by heat-inducing absorbed energy



Energy absorption step
(Schwan-effect, β/δ dispersion)

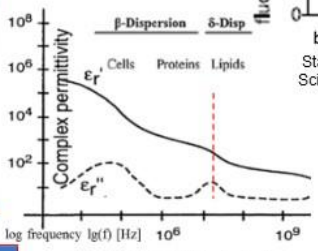


Membrane rafts

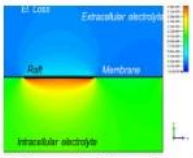


Staunton JR et al,(2008) Scientific Reports, 3:1449

Select & attack membrane rafts

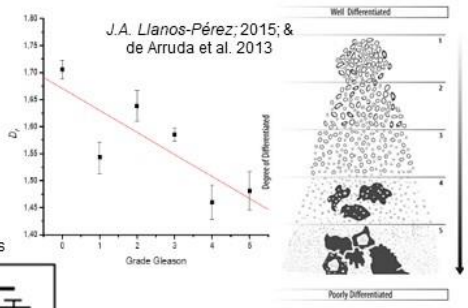


A. Caduff, et.al. Diab. Tech. & Therap., 12(1), 2010



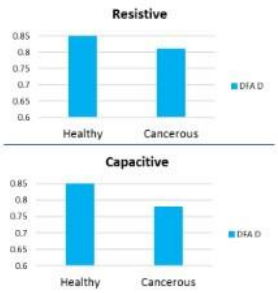
E. Papp, et.al. Open Journal of Biophysics, 2017, 7, 216-229

Homeostatic modulation
(fractal physiology)



Selection by pattern differences

Fractalinity by impedance



Lovelady et. Al. Phys.Rev. E 76 (2007), 041908.

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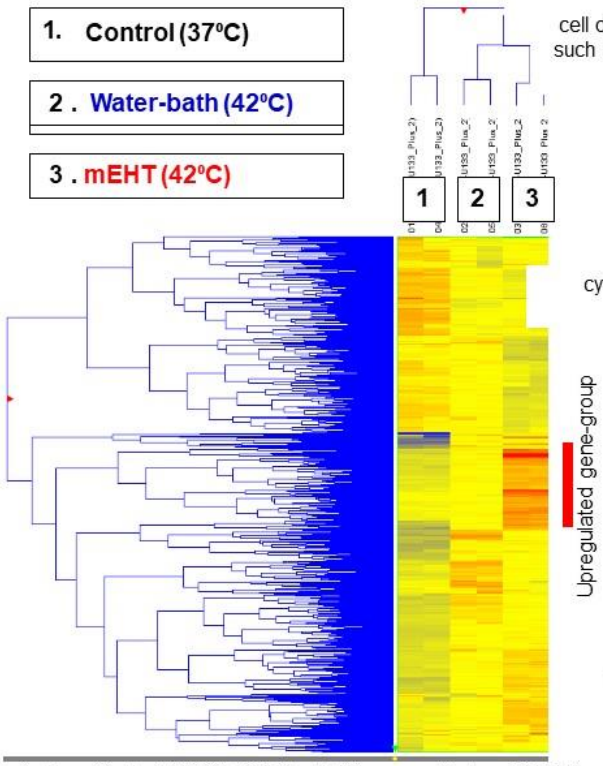
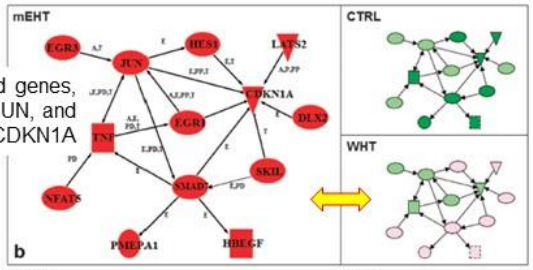
mEHT heats differently (mRNA-based info)

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

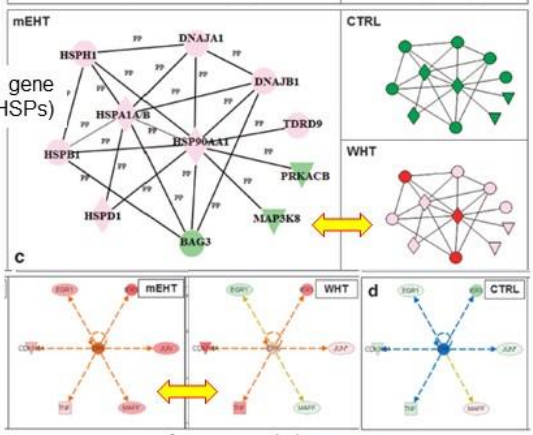
1. **Control (37°C)**
2. **Water-bath (42°C)**
3. **mEHT (42°C)**



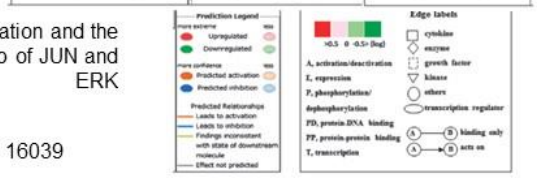
cell death-related genes, such as EGR1, JUN, and CDKN1A



cytoprotective gene network (HSPs)



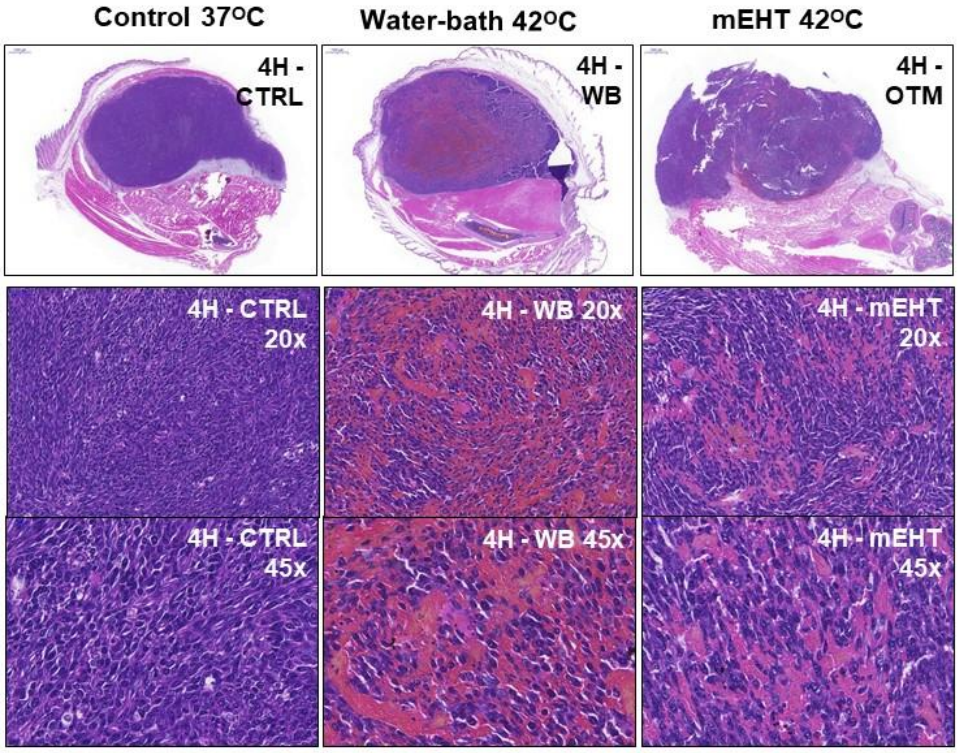
ERK activation and the relationship of JUN and ERK



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

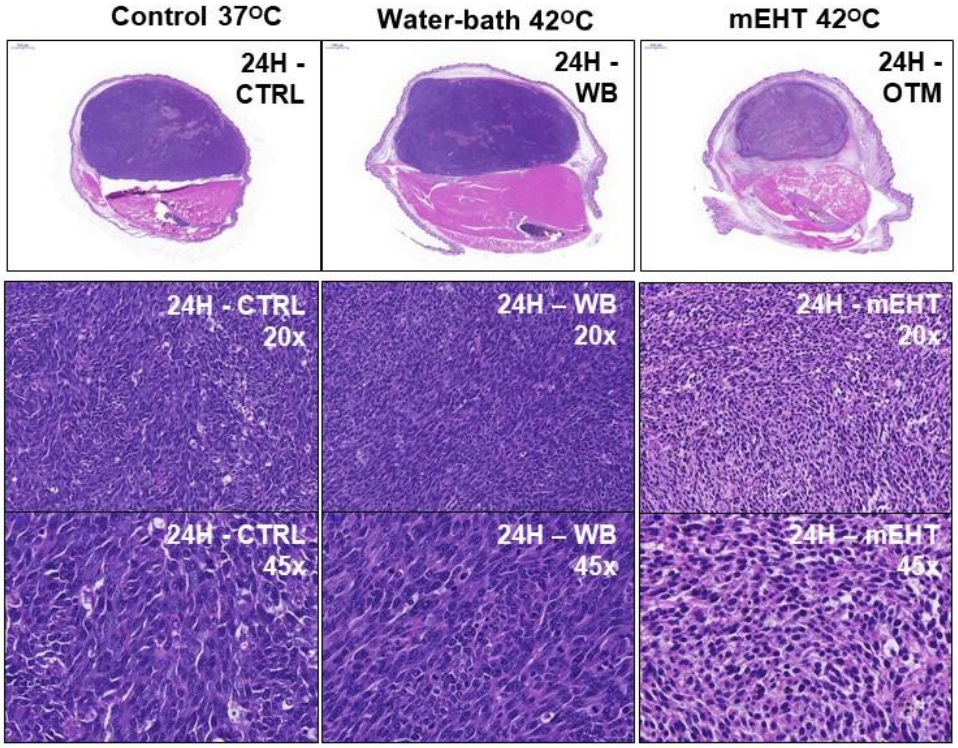
Morphological change after the treatment 4 hours

Andocs G, Kondo T. Toyama University, Japan, (2018)



Morphological change after the treatment 24 hours

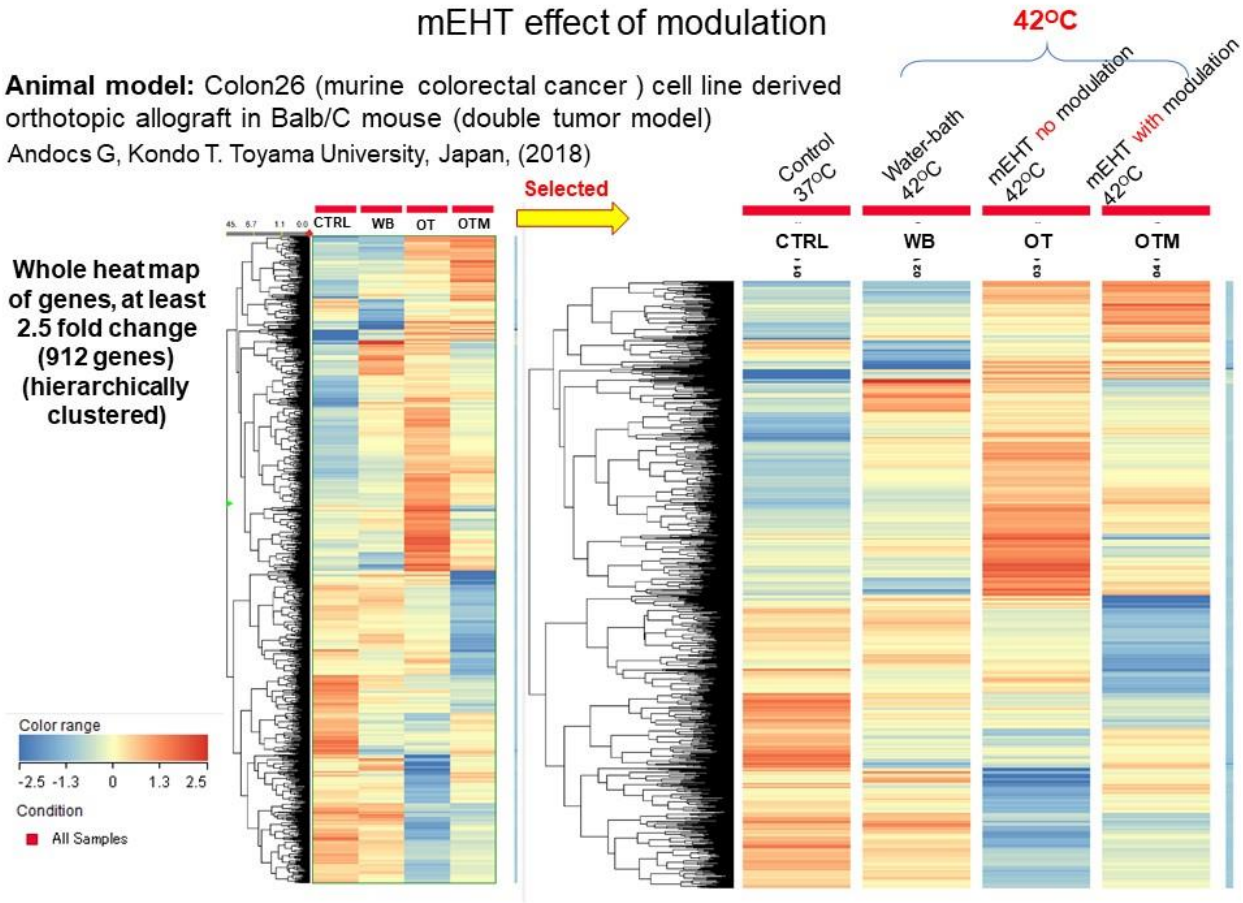
Andocs G, Kondo T. Toyama University, Japan, (2018)



mEHT effect of modulation

Animal model: Colon26 (murine colorectal cancer) cell line derived orthotopic allograft in Balb/C mouse (double tumor model)

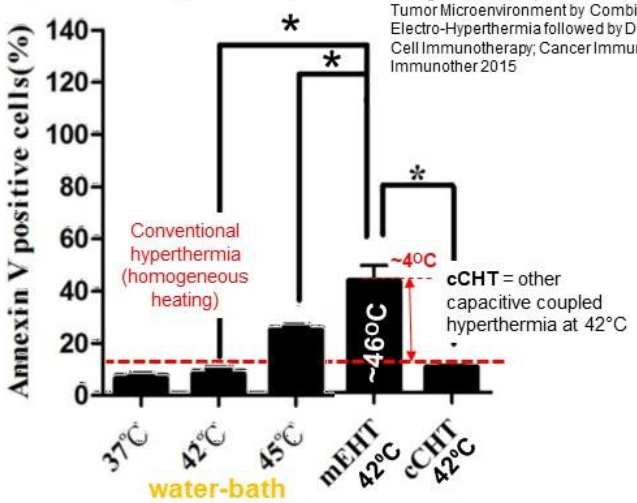
Andocs G, Kondo T. Toyama University, Japan, (2018)



One of the apoptotic pathways (caspase-dependent)

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

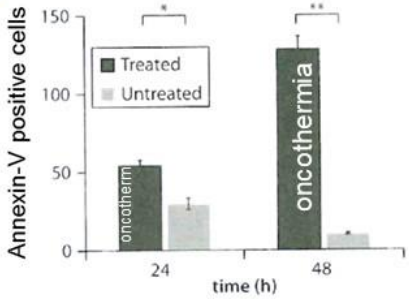


HT29 cells (in vivo)

oncothermia 42ºC

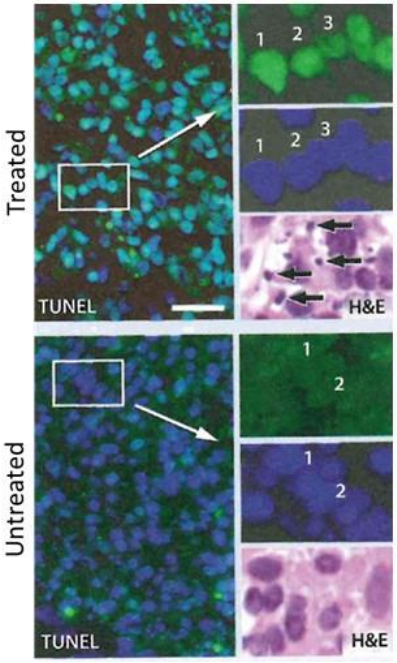
Apoptosis final state

TUNEL

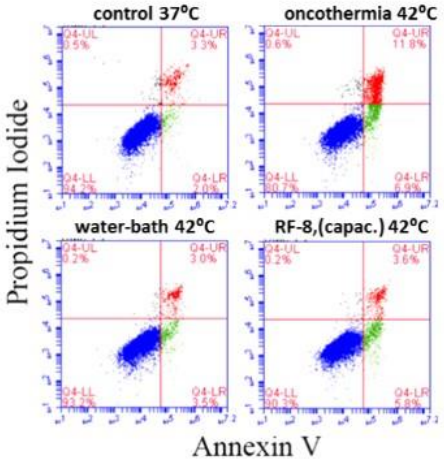


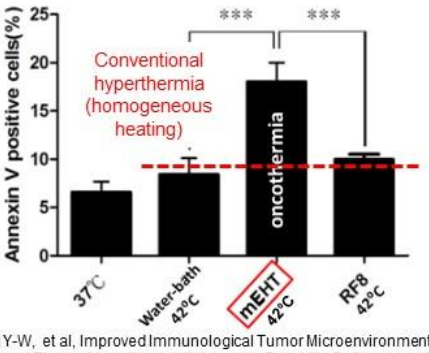
HT29 cells (in vivo)

oncothermia 42ºC



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



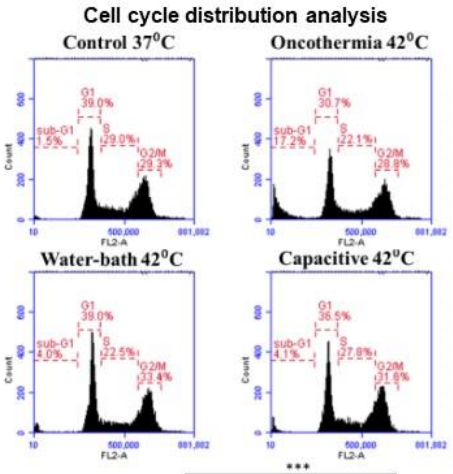


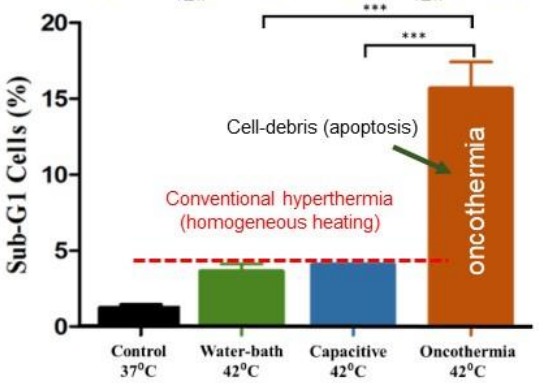
Tsang Y-W, et al, Improved Immunological Tumor Microenvironment by Combined Electro-Hyperthermia followed by Dendritic Cell Immunotherapy; Cancer Immunology, BMC Cancer 15:708, http://www.ncbi.nlm.nih.gov/pubmed/26472466

Apoptosis

HepG2 cells (in vitro)

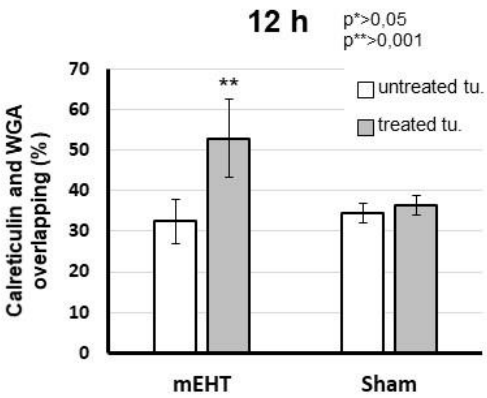
Flow-cytometry

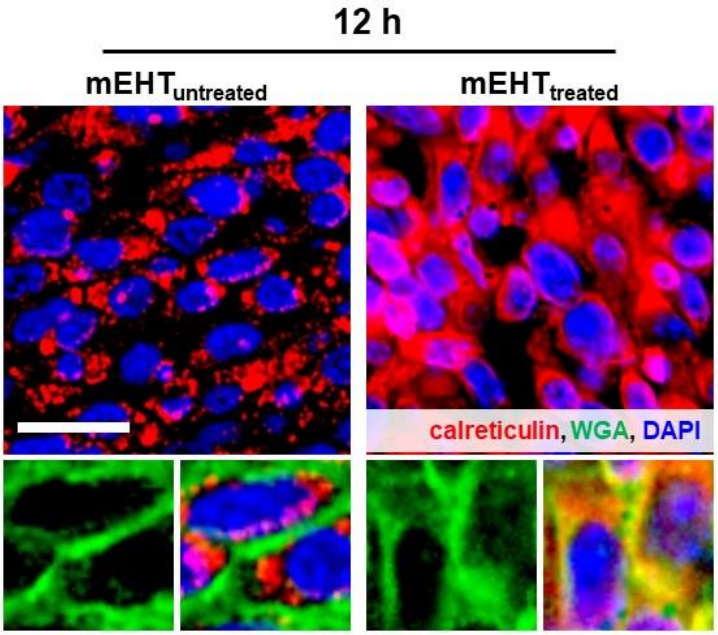




Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et.al. (2016) In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, oi: 10.18632/oncotarget.11444

DAMPs: calreticulin

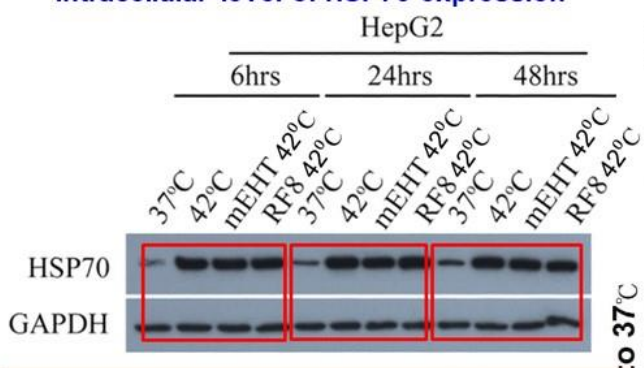




Vancsik T, Kovago Cs, Kiss E, Papp E, Forika G, Benyo Z, Meggyeshazi N, Krenacs T. (2018) Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts, J Cancer, 9(1): 41-53

DAMPs: Comparison of the induced HSP70

Intracellular level of HSP70 expression

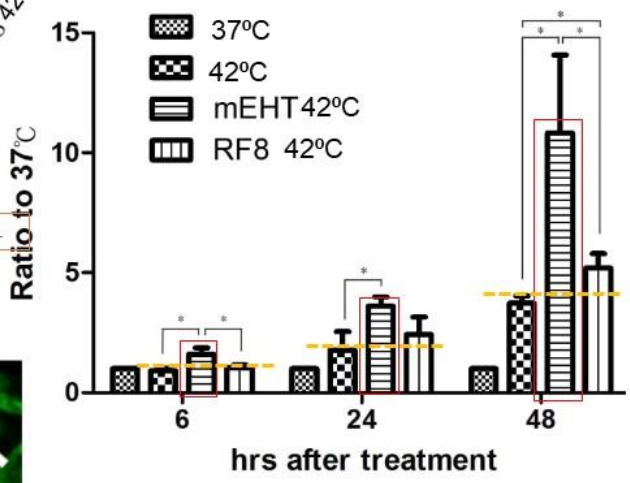


All kinds of hyperthermia could induce intracellular HSP70 expression.

Yang K-L, et.al. (2016), Oncotarget, oi: 10.18632/oncotarget.11444

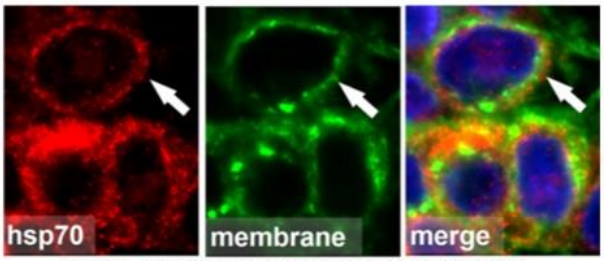
Extracellular level of HSP70 expression

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



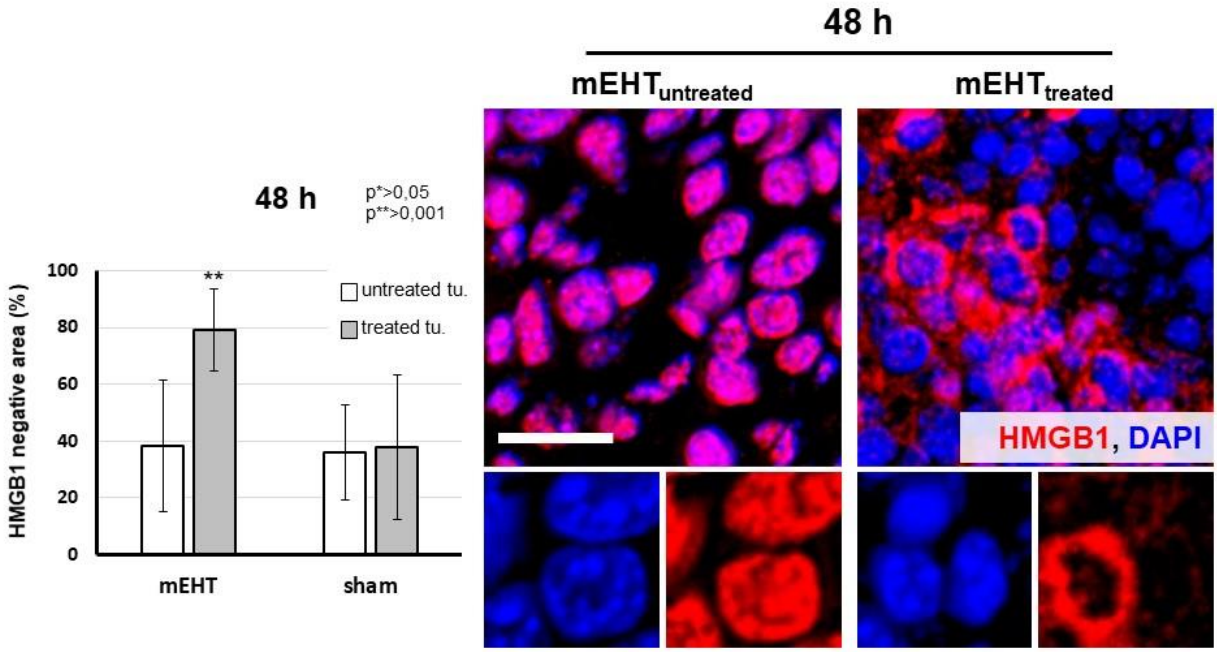
Oncothermia triggered a significantly secretion of HSP70 from cancer cells.

Membrane localization of HSP70 (14h)



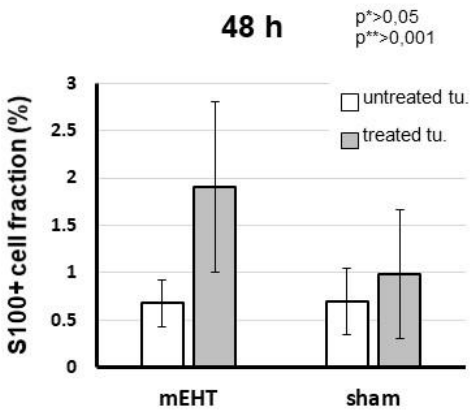
Andocs G, et al. (2014). Cell Stress and Chaperones 20(1):37-46

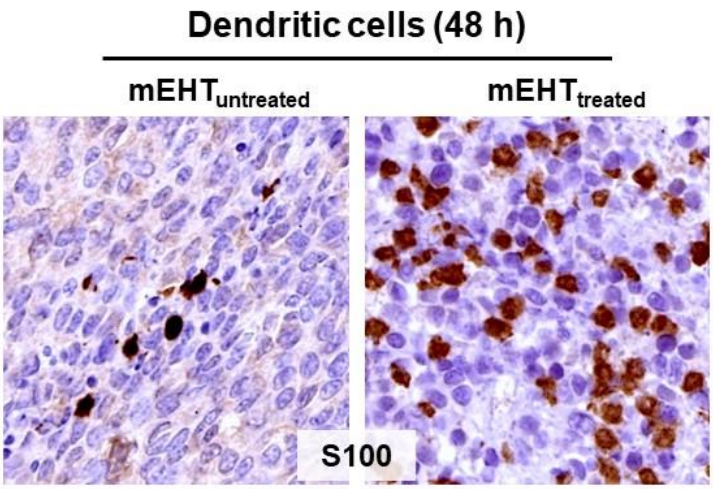
DAMPs: HMGB1



Vancsik T, Kovago Cs, Kiss E, Papp E, Forika G, Benyo Z, Meggyeshazi N, Krenacs T. (2018) Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts, J Cancer, 9(1): 41-53

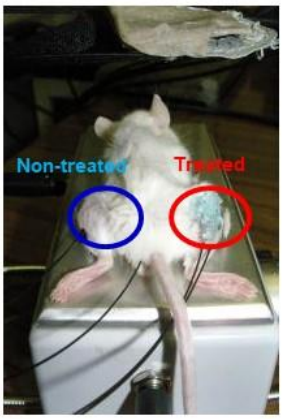
DAMP-process: Antigen presenting cells





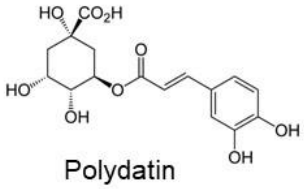
Vancsik T, Kovago Cs, Kiss E, Papp E, Forika G, Benyo Z, Meggyeshazi N, Krenacs T. (2018) Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts, J Cancer, 9(1): 41-53

Abscopal effect by Marsdenia tenacissima

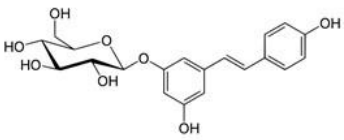


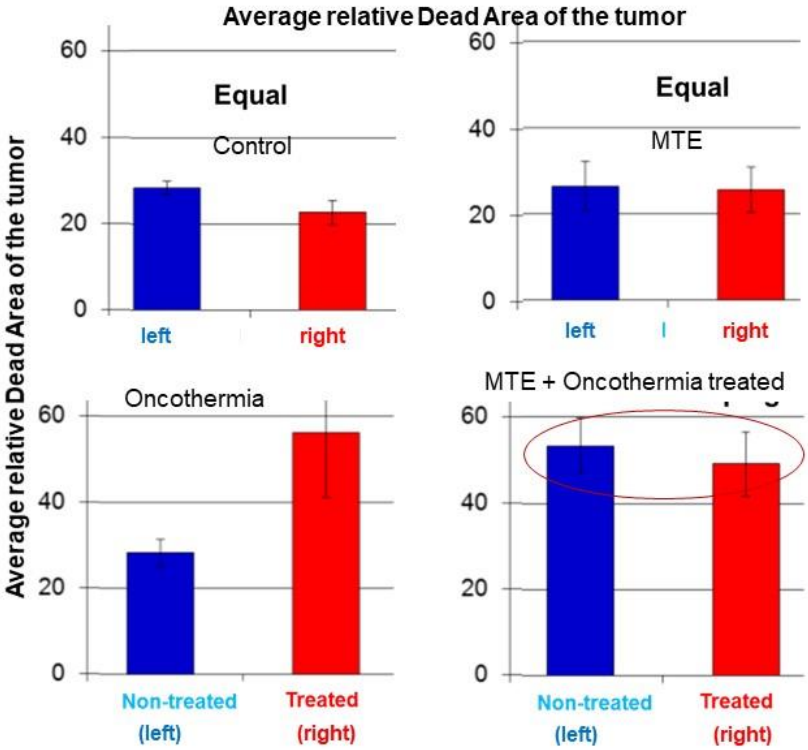
Marsdenia tenacissima (MTE) injection before mEHT

Chlorogenic-acid (11 mg/ml)



Polydatin



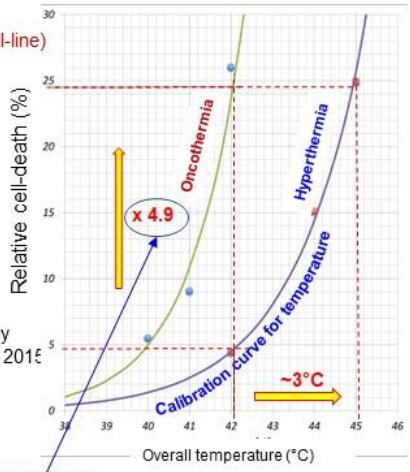


The abscopal effect is clearly proven

Vancsik T, et al (2018) *Journal of Cancer* 9:41-53.

mEHT heats the cell-membrane rafts

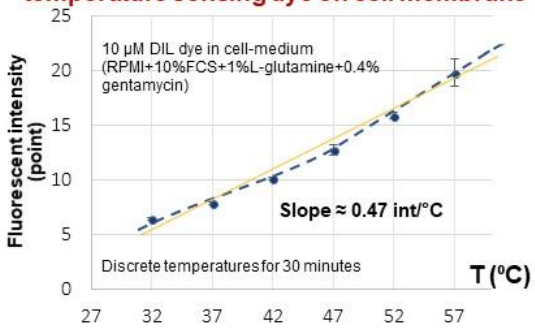
U937
(human lymphoma cell-line)
in-vitro



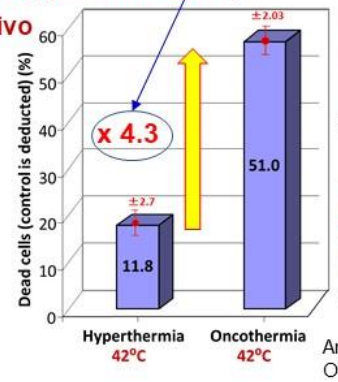
Andocs G, et al. Biology and Medicine 7(4):1-9, 2015

HT29, (human CRC cell-line); in vitro
Vancsik T et al:, 33rd annual Conference of International Clinical Hyperthermia Society (ICHS), Nidda, Germany, July 11-13, 2015

temperature sensing dye on cell membrane



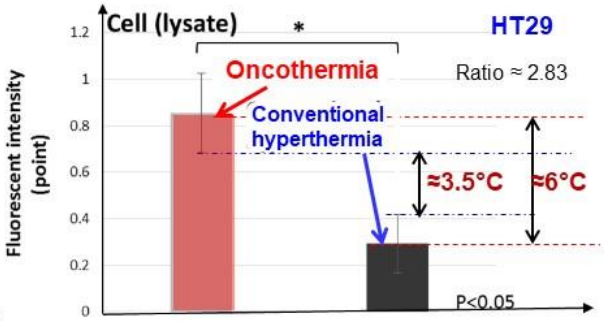
HT29, (human CRC cell-line)
in-vivo



Hyperthermia
42 °C

Oncothermia
42 °C

Andocs G et al: Radiology and Oncology 185:120-26 , (2009)



Oncothermia is thermal

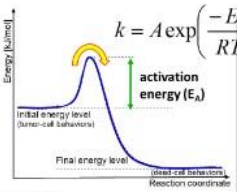
Post-treatment 24 H, 30 min; Each point is 3 independent measurements

In vitro: U937 human lymphoma cell-line (10^6 cell/ml)

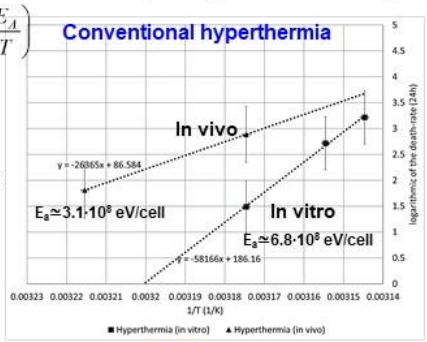
Andocs G, et al, Biology and Medicine 7(4):1-9, 2017,

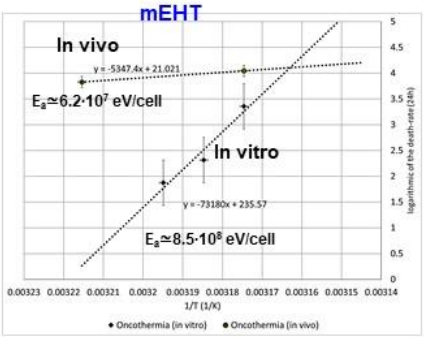
In vivo: HT29 human colorectal cancer xenograft
Andocs G et al. Radiology and Oncology (Strahlentherapie und Onkologie) 185:120-26 , (2009)

$$k = A\exp\left(\frac{-E_A}{RT}\right)$$

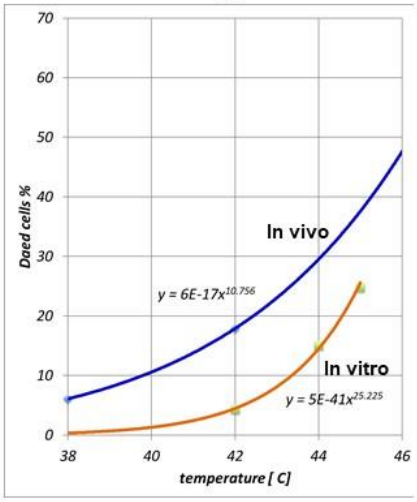


Arrhenius plots (thermal effect)

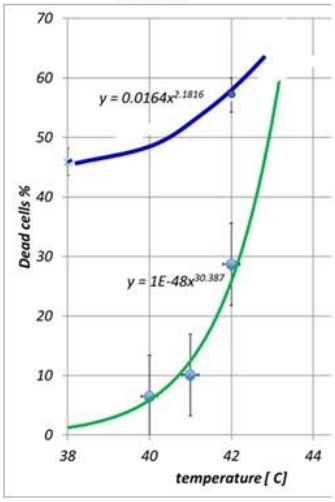




Conventional hyperthermia



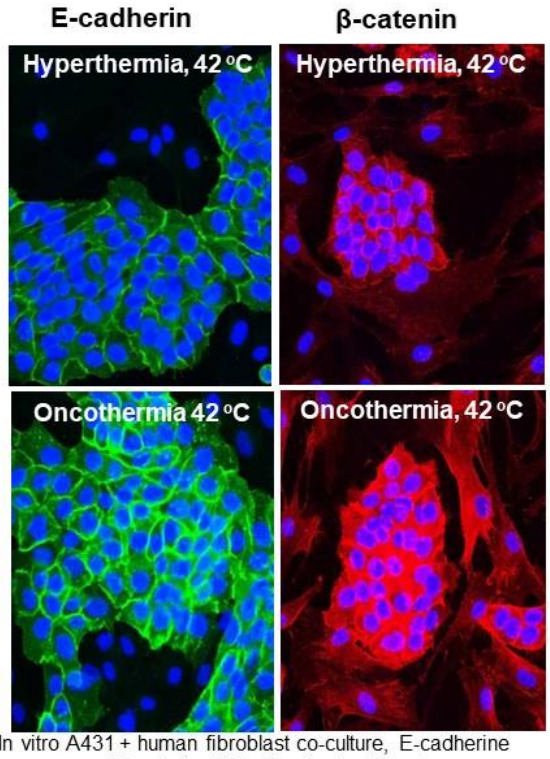
mEHT



Power-function

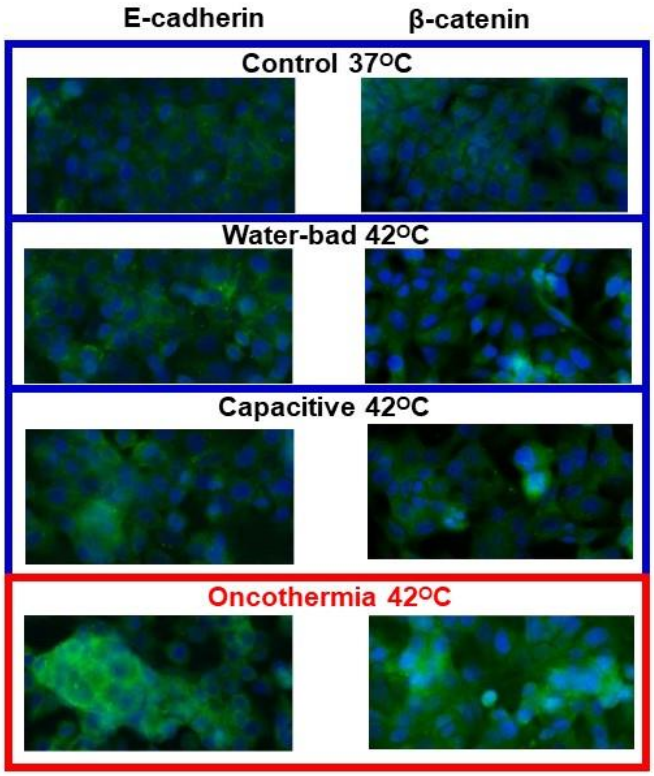
The activation energy is calculated

Block the invasion and dissemination



In vitro A431 + human fibroblast co-culture, E-cadherine and β-catenin; 24h after the treatments

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

Outline

- ❑ **The challenge**
- ❑ **The methods**
- ❑ **Experimental results**
- ❑ **Clinical results**
- ❑ **Conclusions**

mEHT treatment – easy to use and safe

Triple negative locally advanced breast cancer

Investigator: Prof. Chi K-W, Shih-Kong Hospital, Taipei, Taiwan
Presented on 35th ICHS Conference, Guangzhou, China; Nov.2017)

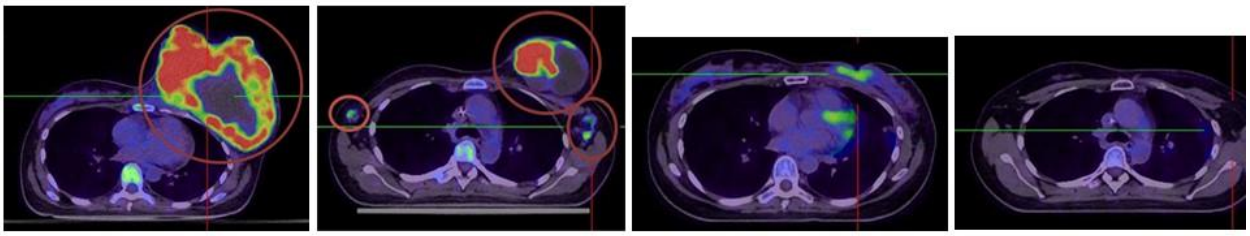
RT 2/22-3/29 total dose 50Gy

4/17-till now (2017) Good response, 5/26 pCR

mEHT for 7 times

2/17 2/22 3/2 3/8 3/15 3/22 3/28

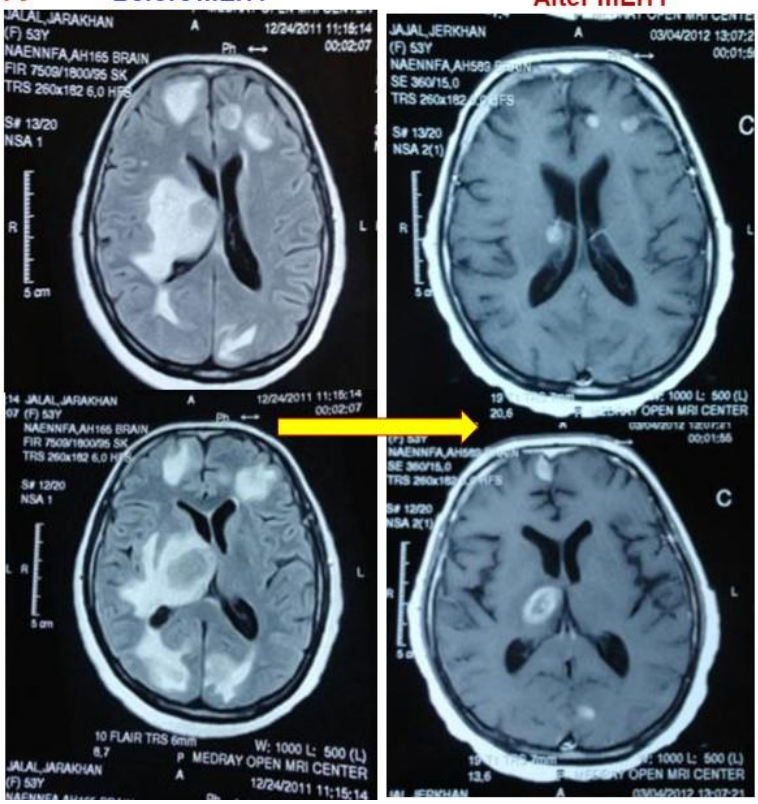
4/20 autoimmune hepatitis



Brain metastasis from breast cancer

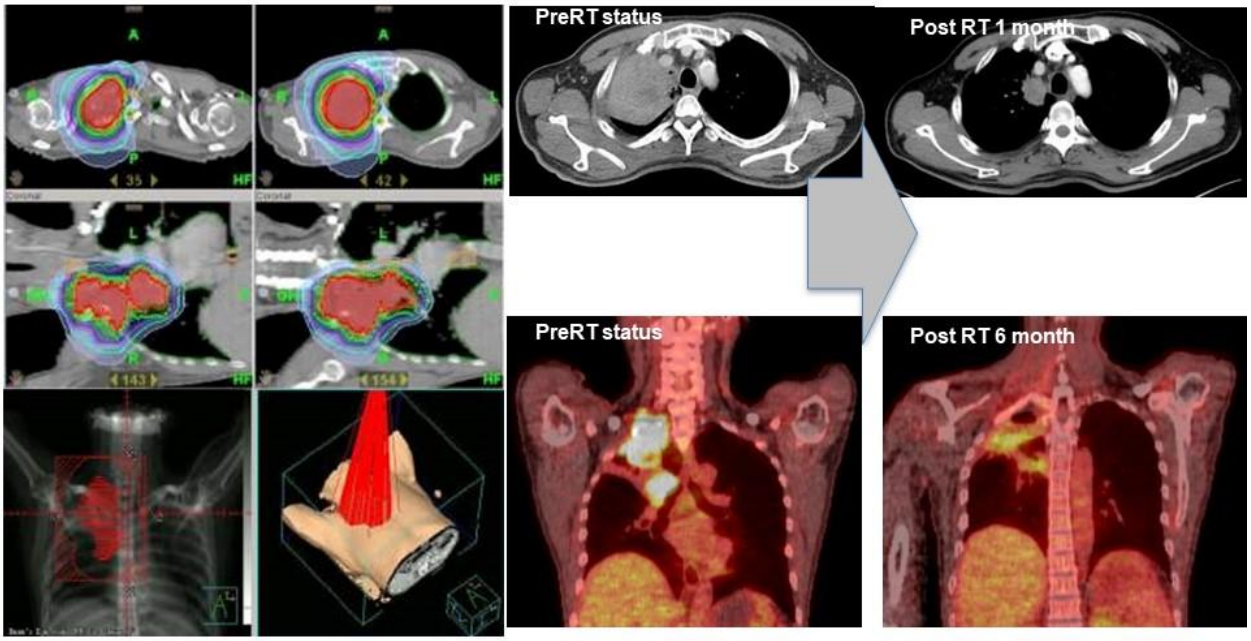
Investigator: Dr. Marwan Akasheh; **Institute:** Dar Alshefa' Tumors Treatment Center, Amman, Jordan, **Patient**: female 53 y.

mEHT Monotherapy **Before mEHT** **After mEHT**



NSCLC Cases

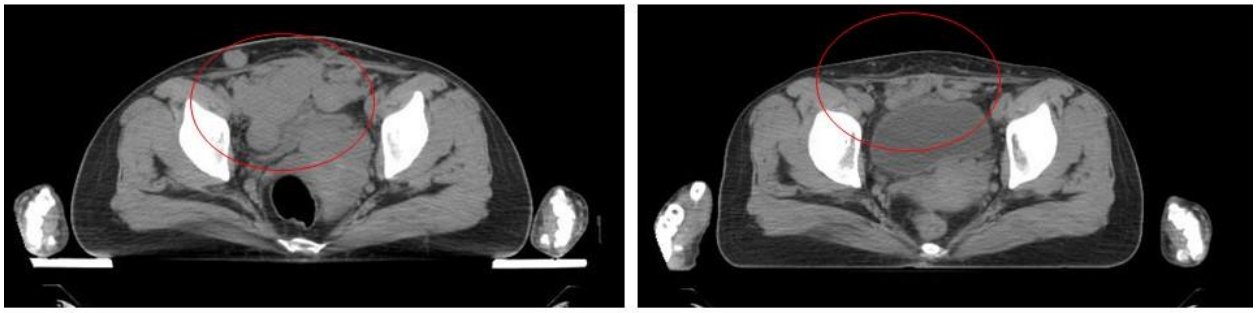
Investigator: Prof.Dr.Chang Geol Lee; **Institute:** Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; **Presented** on KOSG'2013, Jeju
Patient: 51 years old, male patient; **Diagnosis:** NSCLC, RUL, AdenoCa, cT4N3M0; **T :** 6.5x3.7cm, right brachial plexus invasion; **N :** Both SCL, Lt. axillary LN; Referred for CCRT
Treatment: RT: 66 Gy/30 fractions; CTx: weekly paclitaxel/cisplatin; Oncothermia: 10 fractions/5 weeks



Recurrent uterine sarcoma with peritoneal seedings

Investigator: Prof. Chi K-W, Shih-Kong Hospital, Taipei, Taiwan
Presented on 35th ICHS Conference, Guangzhou, China; Nov.2017)

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

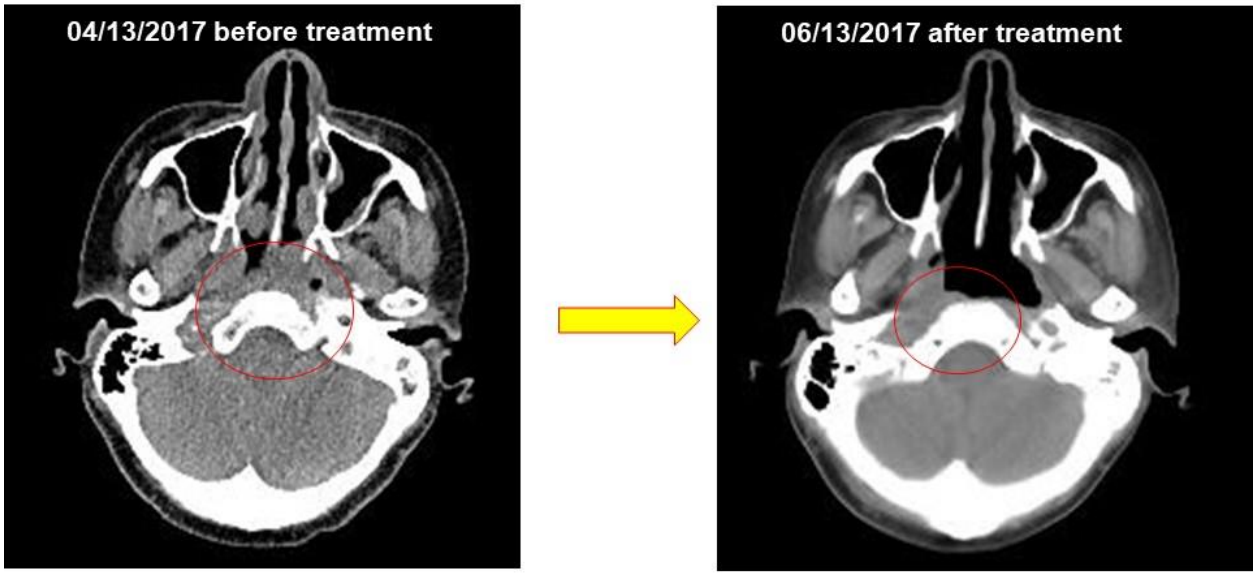


Before treatment → **After treatment**

Intratumoral ipilimumab 2.5 mg, i.v. nivolumab 50 mg and complementary with oncothermia 6 times (1 time/week)

Recurrent nasopharyngeal carcinoma

Investigator: Prof. Chi K-W, Shih-Kong Hospital, Taipei, Taiwan
Presented on 35th ICHS Conference, Guangzhou, China; Nov.2017

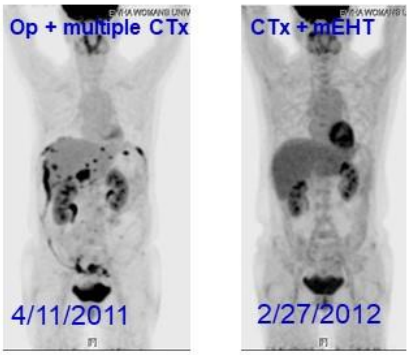


Nivolumab 60mg q3w; RT: 2017/05/01- 6/12:60Gy/30fx; Oncothermia 6x

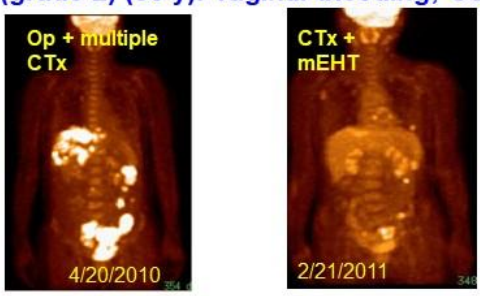
Abscopal effect

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

Recurrent refractive progressive ovarian cancer (55y)

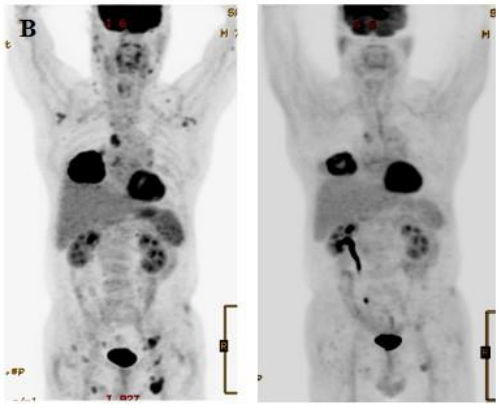


Invasive adenocarcinoma of ovary (grade 2) (33 y). Vaginal bleeding; G5P2



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

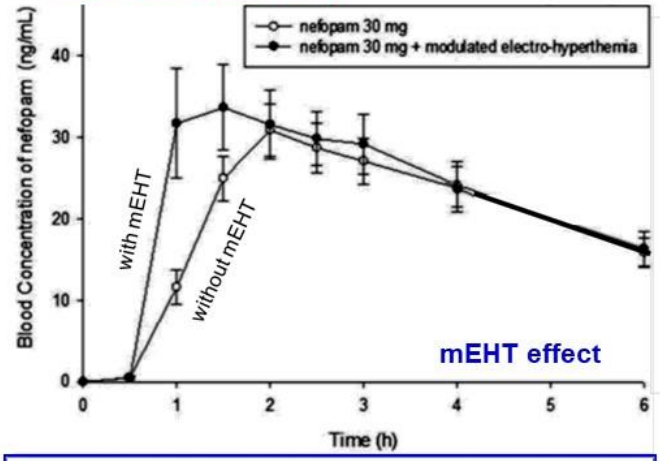
Investigator: Prof. Dr. Seong Min Yoon,
Division of Hematology-Oncology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University, Korea
Patient: SAsc, 72 y, male, Primer-tumor: Non-small cell lung cancer; Size: 9.5 cm right middle lobe; Metastases: in sentinel and distant lymph-nodes; Tumor-classification: cT2 cN2 Mx, stage IIIB
Treatment: 28x1.7 Gy; support: **250 microgram Leukine and Oncothermia 6x**

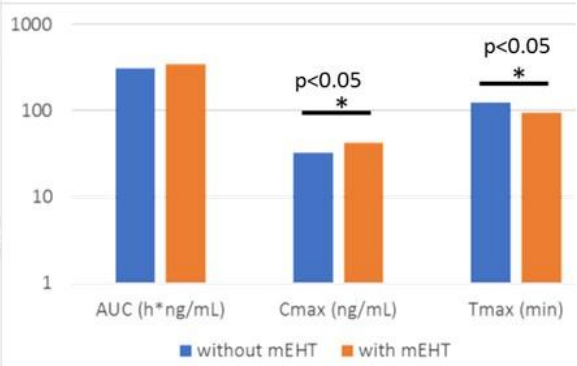


Randomized study (n=6+6) for pharmacokinetics

mEHT (with Nefopam)

Lee SY, Kim M-G (2015); Int J Hyp, 31:869; 2015

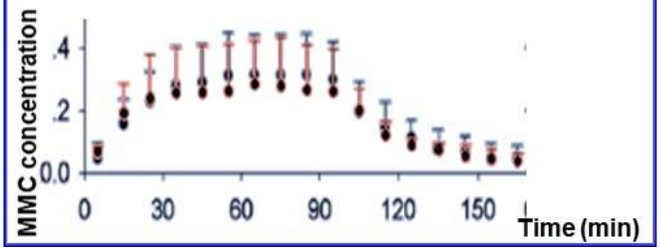




Despite the mild overall heating mEHT significantly increases the maximum of the kinetic curve (C_{max}) and also significantly decreases the time at maximum (T_{max}) parameters. The area under the peak (AUC) was stable, indicating the unchanged systemic adverse effects, despite the increase of the absorption of the drug.

Conventional hyperthermia (with Mitomycin-C)

Sørensen O, et al. (2014) Impact of Hyperthermia on Pharmacokinetics of Intraperitoneal Mitomycin C in Rats …, Journal of Surgical Oncology;109:521–526

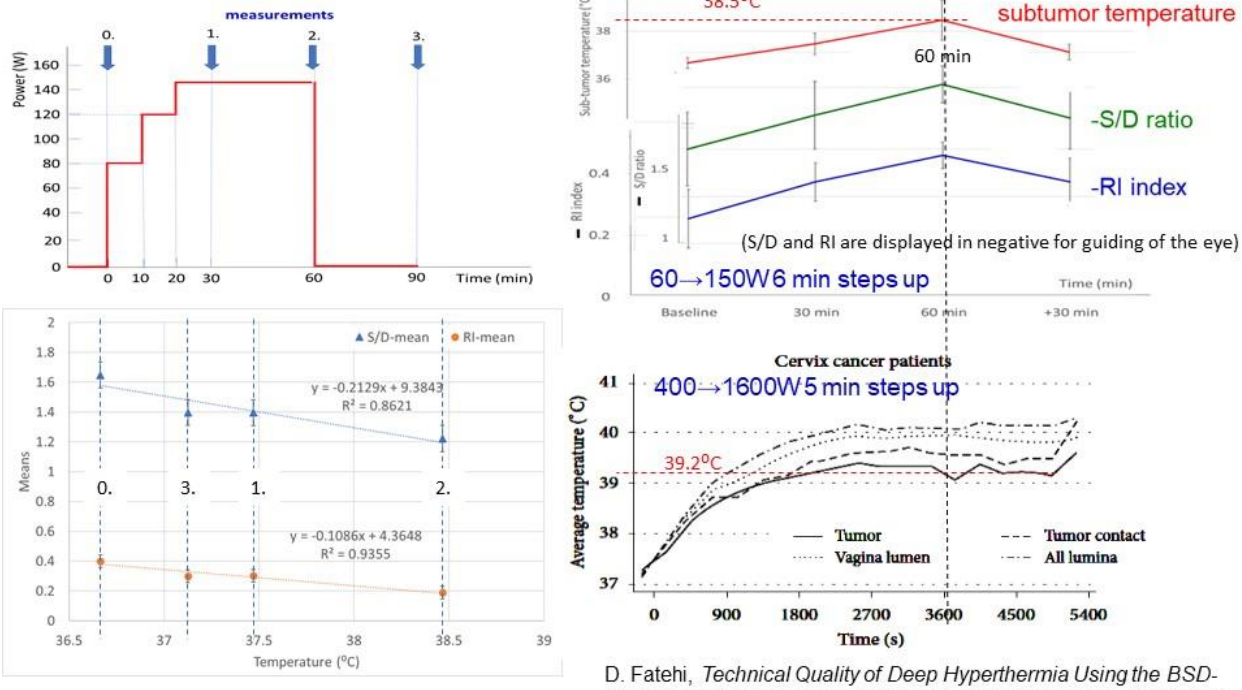


This effect depends on the permeability of the vessel-wall, which is increased by the applied electric field.

Prospective study (n=20) for blood-flow changes in cervix

Biopsy proven cervical carcinoma by mEHT therapy. **Peri-tumor temperature**: internal organ temperature probe. **Tumor blood flow**: by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels. (3D color Doppler ultrasound)

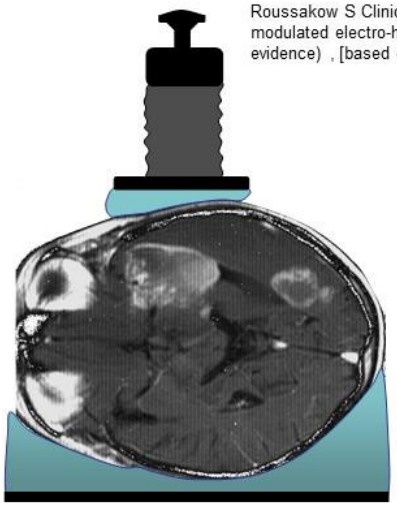
Lee S-Y, Kim JH, Han YH, Cho DH; Int. J. Hyperthermia, Jan 3:1-24, (2018)

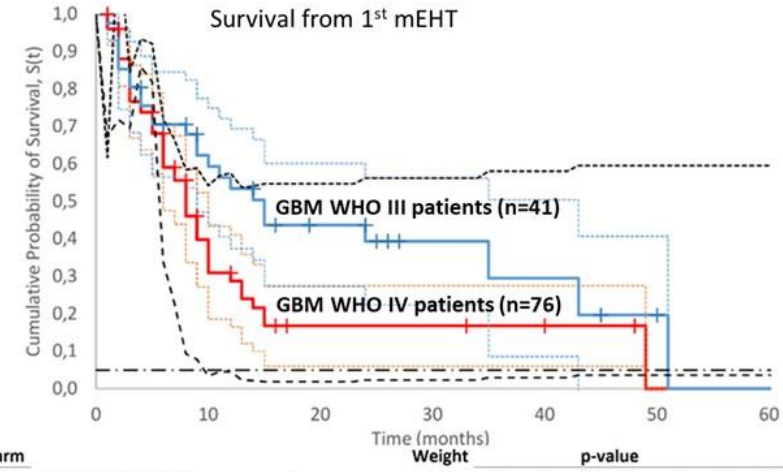


D. Fatehi, *Technical Quality of Deep Hyperthermia Using the BSD-2000*, Uitgeverij Box Press, Oisterwijk, The Netherlands, 2007, PhD.

Recurrent glioblastoma multiforme meta-analysis

Roussakow S Clinical and economic evaluation of dose-dense temozolomide 21/28d regimen with and without concurrent modulated electro-hyperthermia in the treatment of recurrent glioblastoma: a retrospective comparison of cohort trials (2a level evidence) , [based on Publications of Gronemeyer et al. (2004)]; BMJ Open, 7:e017387.doi.1136/BMJ-open-2017-017387; (2017).





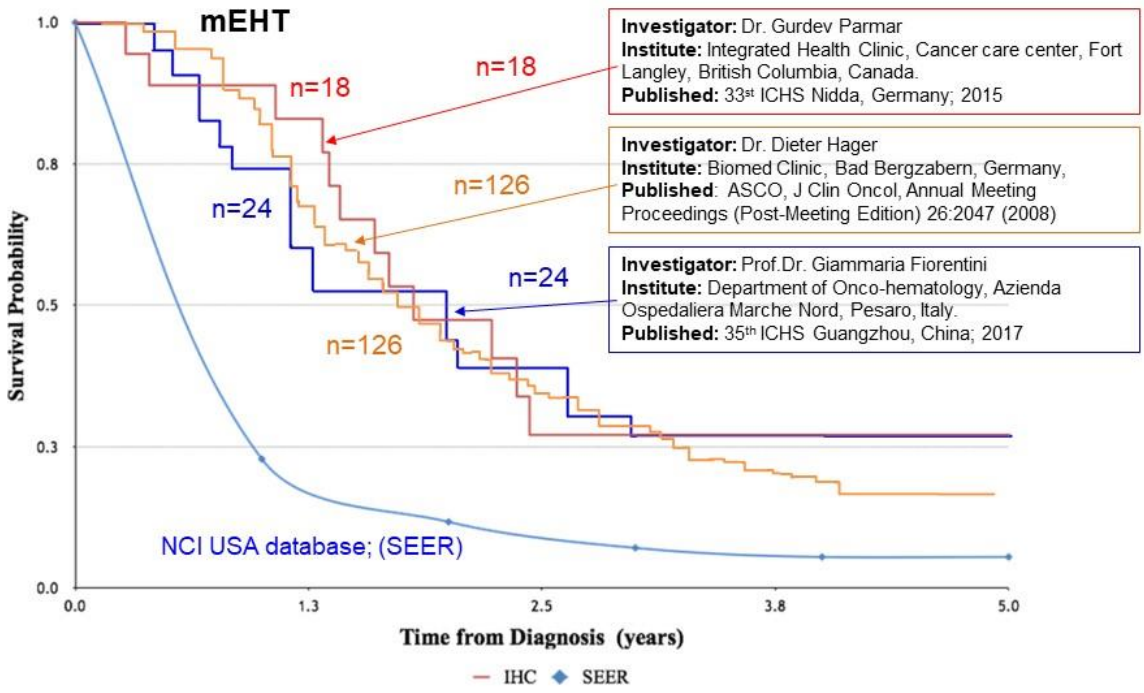
No Study, cohort	Single-arm M/No	Mean survival time	Weight (%)	p-value 1	2	3	4	5	6	7
1 Jungk (2016), BCNU	9,0/34	9,00 (7,49 – 10,51)	10,6%	1,00	0,00	0,00	0,87	0,98	0,61	0,07
2 Reithmeier (2010), BCNU	5,1/35	5,10 (4,48 – 5,72)	62,6%	0,00	1,00	0,14	0,03	0,00	0,00	0,05
3 Glas (2009), ACNU + VM26	6,0/35	6,00 (5,01 – 6,99)	24,4%	0,00	0,14	1,00	0,12	0,02	0,00	0,37
4 Heiland (2016), BEV + CCNU	8,7/18	8,70 (5,51 – 11,89)	2,4%	0,87	0,03	0,12	1,00	0,90	0,62	0,33
5 Hau (2010), ACNU+mEHT, salvage	9,0/15	8,96 (6,69 – 11,23)	4,7%	0,98	0,00	0,02	0,90	1,00	0,65	0,16
6 Douwes (2005), ACNU+mEHT	9,7/19	9,68 (7,61 – 11,75)	5,6%	0,61	0,00	0,00	0,62	0,65	1,00	0,04

Random effect model (I^2=0,0%, p=0,59)

0 5 10 15
Mean ST, months
worst ← → better

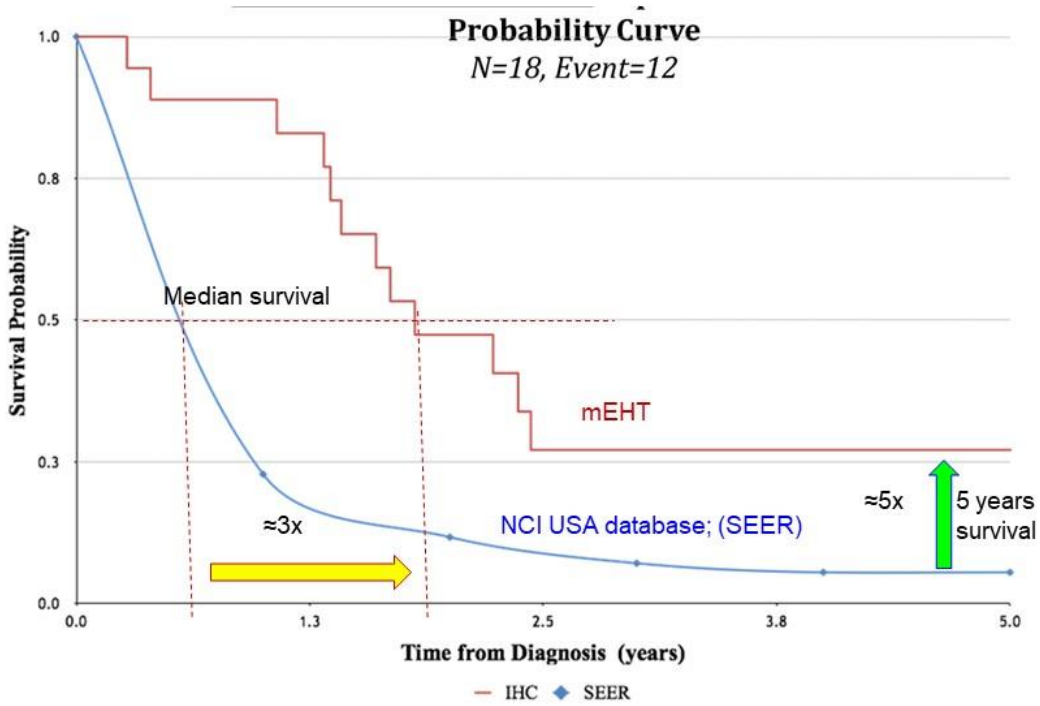
Glioblastoma multiform – comparison of three survival results

Overall survivals

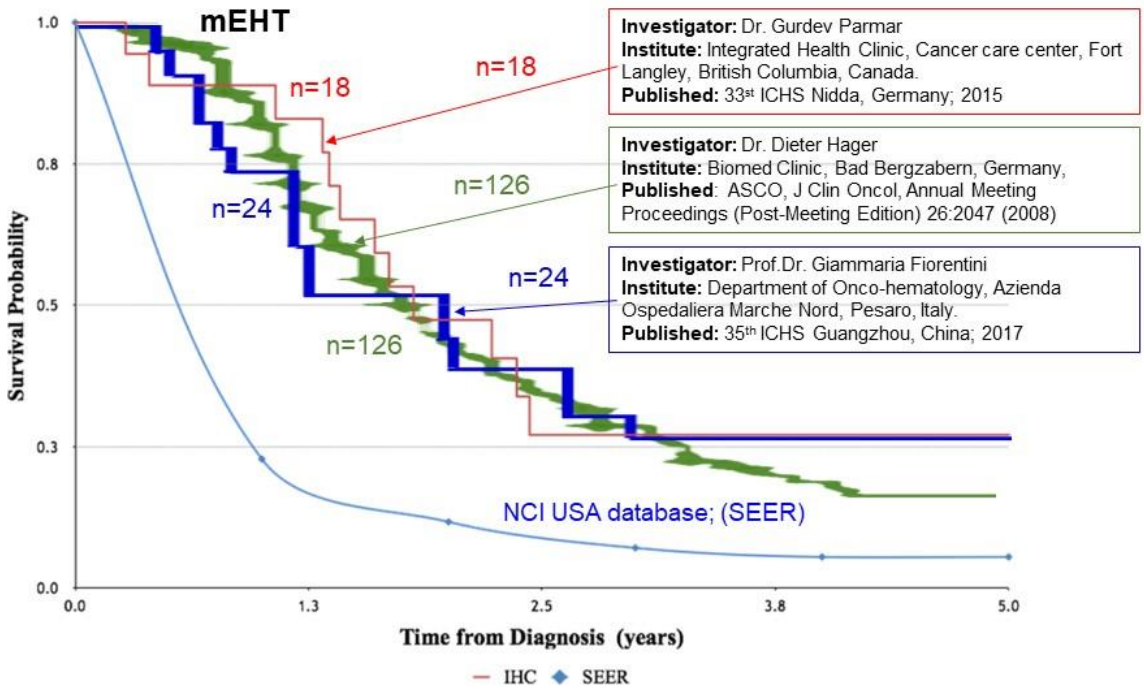


Glioblastoma multiform

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



Glioblastoma multiform – comparison of three survival results

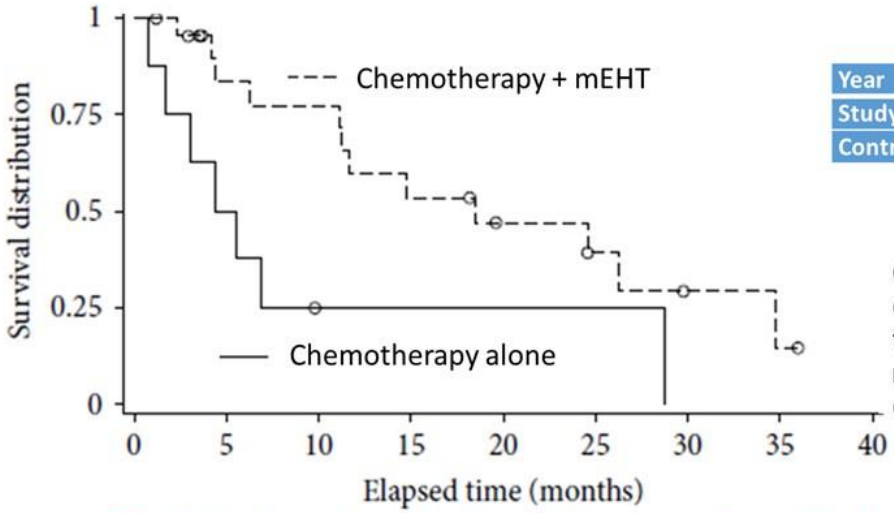


Small-cell-lung-cancer (n=9+10) double arm prospective study

Investigator: Professor DY Lee, Kagnam Severance Hospital, Yonsei University, Seoul, S.Korea

Published: Lee DY, et al. (2013) Conference Papers in Medicine, Vol.2013, Article ID 910363, pp.1-7

Prospective, monocenter, cohort double-arm study of chemotherapy with and without complementary oncothermia
Chemotherapy 1st line (n=28): Irinotecan (60 mg/m^2), Cisplatin (60 mg/m^2) three times.
Chemotherapy 2nd line (n=19): Etoposide, (110 mg/m^2) Cisplatin (70 mg/m^2)
Additional oncothermia in 2nd line combination (n=9): 150 Watt, 1,490.5 kJ, 60 min, every second day, with rise in temperature to 38.5°C–42.5°C. Electrode 30 cm diameter at least 12 sessions were in 1 cycle.



Local control

Year	1	2
Study arm	59.0%	47.0%
Control arm	25.0%	25.0%

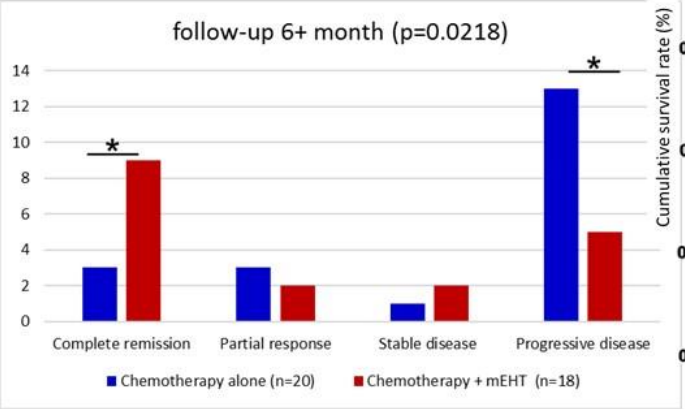
Conclusion: the local control and the survival time are successfully managed together in small-cell-lung carcinoma

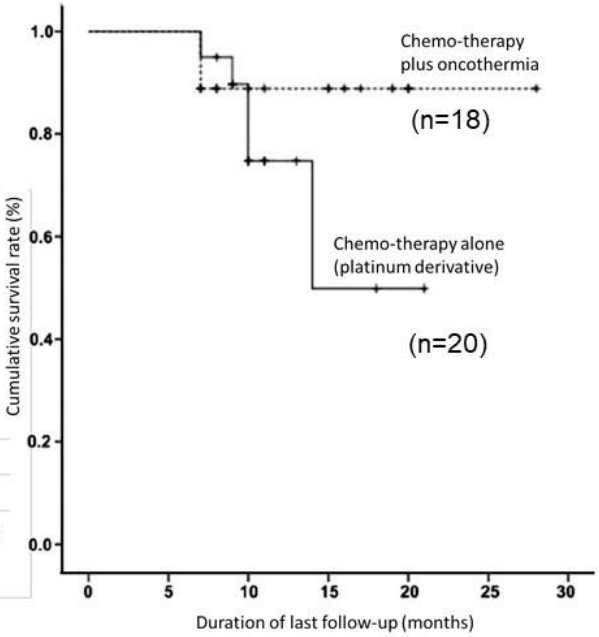
Both the local control and the overall survival are improved

Recurrent cervix double arm (n=20+18), randomized study

Lee SY, Lee NR, Cho D-H, Kim JS; Oncology Letters, ttps://doi.org/10.3892/ol.2017.6117, (2017)

Patients received conventional chemotherapy alone (n=20) compared to the combination to mEHT (n=18). Every patient had chemotherapy [paclitaxel + cisplatin (n=14), paclitaxel + carboplatin (n=10), cisplatin + 5-fluorouracil (n=12), cisplatin alone (n=2)]. Radiotherapy was not possible in this cohort.





Both the local control and the overall survival are improved

Phase III randomised cervix trial (n=236) of mEHT with RT (interim results (n=160), follow-up is ongoing)

Investigators: Minnaar CA; Kotzen JA; Baeyens A. Charlotte Maxeke Johannesburg Academic Hospital, S.Afrika. **Aim:** to enrol 236 participants with FIGO stage IIB (initial distal parametrium involvement) to IIIB cervical cancer

Statistics	n	%
HIV positive	120	51%
Stage III	157	66.6%

Radiation: 25x2Gy external and 3x8Gy brachytherapy

Chemotherapy: 3x 80mg/m2 Cisplatin

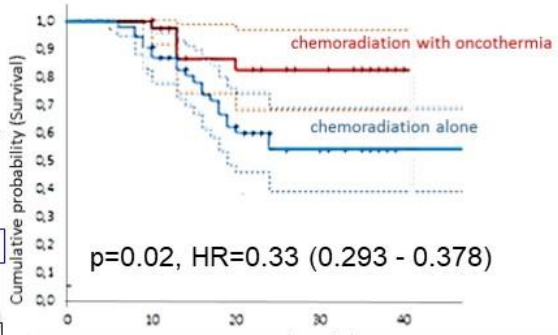
mEHT (oncothermia): 2x 55min/week (4 weeks)

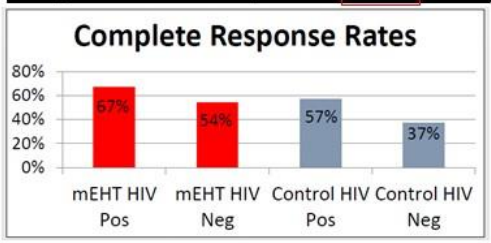
Local control

Until now: 6 month Local Disease Control
160 patients completed 6 month PET scan.

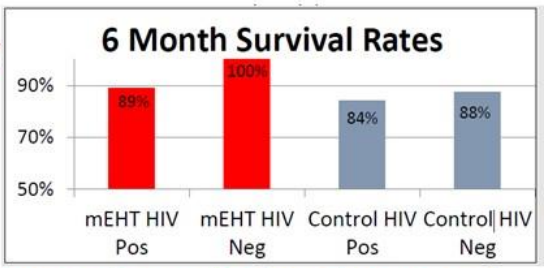
Measured	Radio-chemotherapy				Gain by mEHT (%)
	with mEHT		without mEHT		
	n	%	n	%	
Complete response	33	47%	27	32%	15%
6 months survival (n=160)	70	91%	90	81%	10%
24 months survival (n=114)	55	78%	59	65%	13%
Progression Free survival	53	76%	55	61%	15%

Survival time control





Interim report by HIV infection (subgroups)

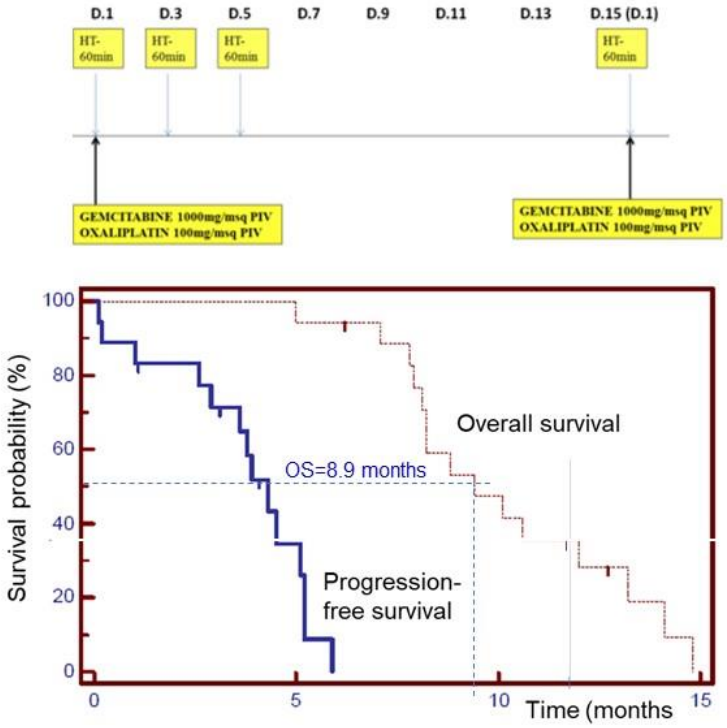


Until now, both the local control and the overall survival are improved

Pancreas Phase II study (n=26)

Metastatic pancreatic cancer with progressive disease after gemcitabine treatment. In the 2nd line the patients received gemcitabine 1000mg/m^2 IV and oxaliplatin 100mg/m^2 IV day 1 (GEMOX) combined with mEHT days1, 3 and 5 all repeated at 14 days

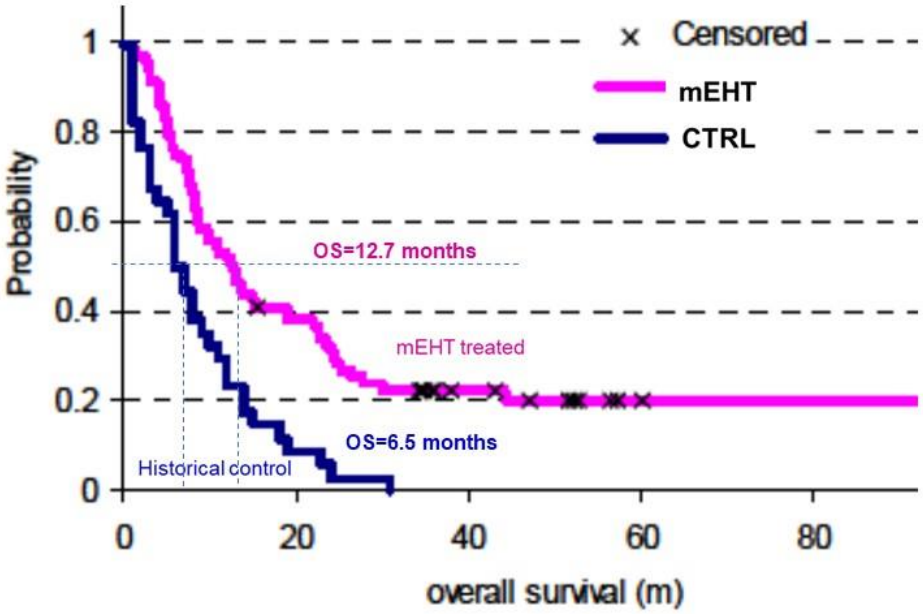
Characteristics	Enrolled (n=17)
Male	9
Female	8
ECOG Performance status	
ECOG 1	5
ECOG2	12
Stage at study entry	
Liver metastasis	6
Lung metastasis	4
Lymph node metastasis	6
Peritoneal carcinosis	4
Bone metastasis	6
Ascites/pleural effusion	8
Nr. of prior chemotherapy cycles (GEM) - median	5.4
Histopathologic types	
Duct cell carcinoma	11
Acinar cell carcinoma	1
Papillary mucinous carcinoma	2
Signet ring carcinoma	1
Adenosquamous carcinoma	1
Undifferentiated carcinoma	1
Prior regional therapy	
Surgery	6
Radiotherapy	3



Volovat et al.; (2014); *Romanian Reports in Physics, 66:166–174*

Advanced, metastatic pancreas Phase II study (n=99)

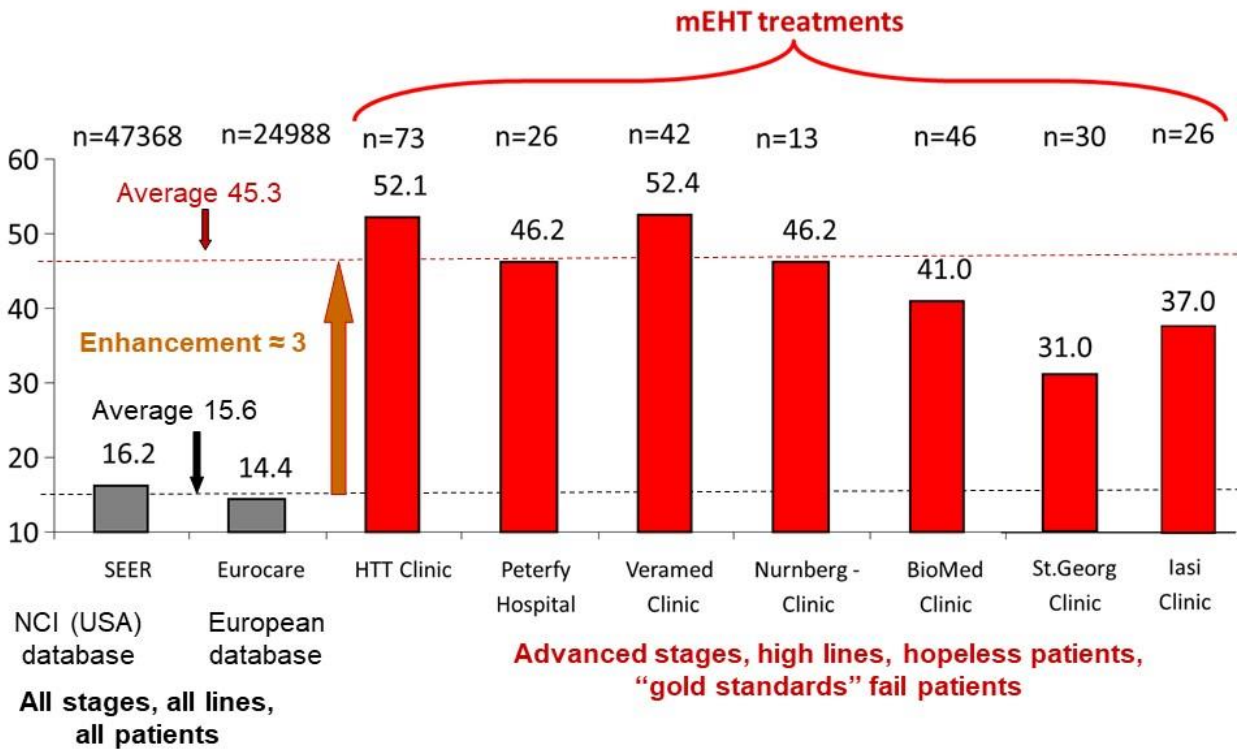
Phase II retrospective, two centers (A & B), single-arm clinical trial (n=99) for advanced pancreas cancer treated by oncothermia [1], Most of the patients had distant metastases (77, 77.8%; A:23,88.7%, B:54,74%) and 40+% had multiple metastases. The trial includes a cohort of heavily pretreated patients (3+ lines), and due to the refractory or another fail of the conventional therapies, in this study mEHT was applied as monotherapy. The first and subsequent year survivals were: 1st:50.5%, 2nd: 27.3%, 3rd:15.2%, 4th:8.1%, 5th:3%. These values are significantly higher than the values from the large databases (SEER and Eurocare). The center B had the historical arm of conventional therapies (and palliation) of the cohort, with median overall survival 6.5 m, while the median in active study arm was 12.7 m.



Dani A, et al. (2008) Forum Hyperthermie 1:13–20

Comparison of pancreas studies

Metastatic pancreas CA 1y survival [%]



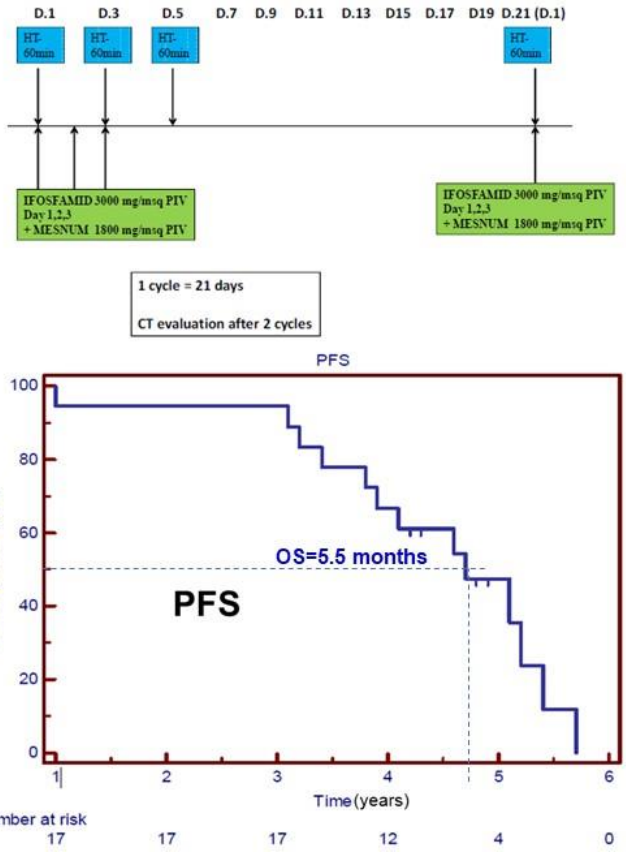
Advanced, high risk recurrent sarcoma Phase II study (n=24)

After recurrence of first line chemotherapy with doxorubicin new line of chemotherapy (ifosfamide 3000mg/m^2, day 1–3) and mEHT (1 hour application with temperature between 41.5°C and 42°C, 3 days/week).

The response 88% (partial response 44% patients for 4 m; stable disease 44% patients for 4 m and 5% only 1 m).

Characteristic	Nr. of patients
Performance status	
ECOG 2	4
ECOG 3	14
Site of metastasis	
Lung	8
Liver	11
Bone	7
Hystopathologic Type	
Fibrosarcoma	5
Mixofibrosarcoma	2
Synovial sarcoma	3
Leiomyosarcoma	3
Epithelioid Sarcoma	2
Angiosarcoma	3

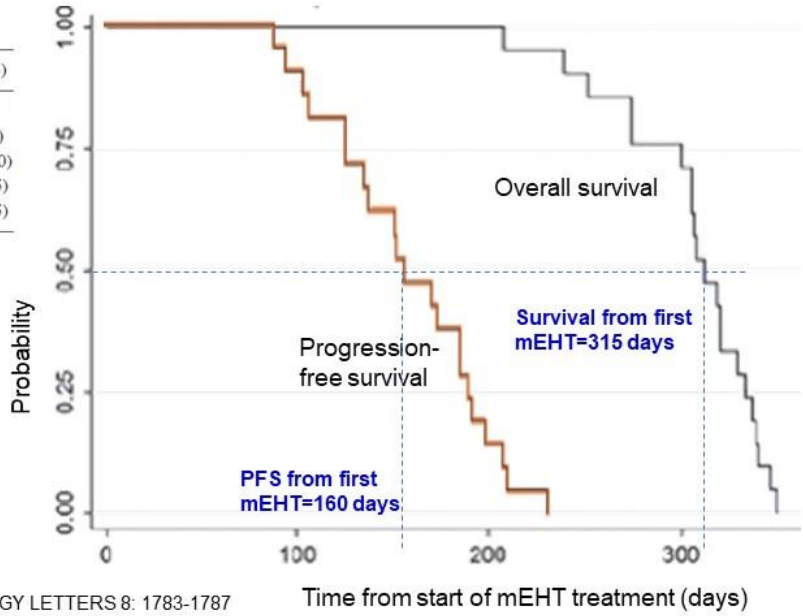
Volovat et al.; (2014) The results of combination of ifosfamid and locoregional hyperthermia (ehy 2000) in patients with advanced abdominal soft-tissue sarcoma after relapse of first line chemotherapy, *Romanian Reports in Physics, 66:175–181*



Hepatocellular carcinoma Phase II study (n=21)

A mono-institutional uncontrolled phase II trial was conducted on advanced HCC patients. Treatment was continued until disease progression (PD) or unacceptable drug-related toxicities. Sorafenib treatment interruptions and dose reductions (initially 200 mg twice daily, then reduced to 200 mg once daily) were allowed for drug-related toxicity.

Response	n (%)
Complete response	0
Partial response	1 (5)
Stable disease	11 (50)
Progressive disease	9 (45)
Disease control rate	9 (45)



Gadaleta-Cardarola G. et al.; (2014); ONCOLOGY LETTERS 8: 1783-1787

Side effects, contraindications of oncothermia

Applicable in most of the cases when gold-standards and/or conventional heat-therapies are not obtainable

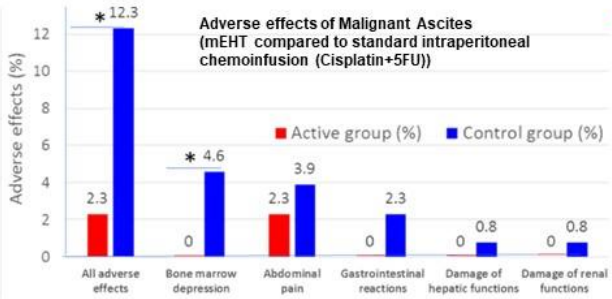
Side effects

- Light erythematic redness (<8%)
- Surface burn (very rare)
- Adipose burn (<3%)

Oncothermia does not gain (mostly suppresses) the side-effects of other complementary applied therapies

Sorafenib and locoregional deep electro-hyperthermia in advanced hepatocellular carcinoma. Adverse events (fatigue, diarrhea), **are commonly associated with Sorafenib.**

Gadaleta-Caldarola G, et al Oncol Lett, 2014 Oct,8(4):1783-1787



Pang CLK et al; Clinicaltrial.gov, Identifier: NCT02638051, 2015, Molecular and Clinical Oncology, 6:723-732, 2017

Side effects	mEHT side effects (glioma treatment)	Rel. val.
Short term asthenia after treatment (< 2 h)		9 %
Local redness (rubor) of the skin		8 %
Subcutanous fibrosis of fatty tissue		1 %
Skin burn (diameter < 1.5 cm) Grade I–II		2 %
Headache and vomiting (< 2 h)		12 %

Sahinbas H, et al. Deutsche Zeitschrift fuer Onkologie 39:154–160, 2007

Contraindications

- Organ transplants or vanished immune-reactions
- Missing thermal sensing
- Inability to communicate
- Woman in pregnancy
- Pacemaker or other electric implants (?)

Sedation, analgesia or anesthesia is not allowed when oncothermia is applied!

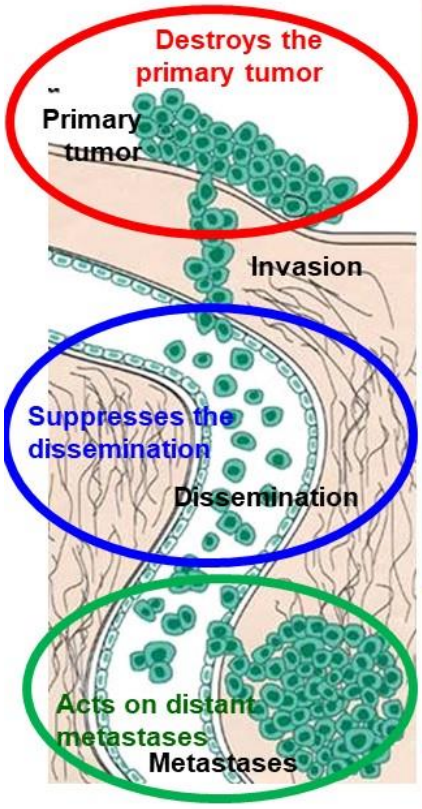
High care is necessary

- Epileptic or electric sensitivity
- Ascites or other free-electrolytes
- Large metallic implants

Outline

- ❑ **The challenge**
- ❑ **The methods**
- ❑ **Experimental results**
- ❑ **Clinical results**
- ❑ **Conclusions**

mEHT results/hot-topics



Selectively destroys the malignant cells with high metabolic rate
Szasz A, et al. Magneto- and electro-biology 22(2):103–115, (2003)
Induces massive apoptosis (produces apoptotic bodies)
Meggyeshazi N, et al. Strahlenther Onkol 190:815-822, (2014)
Apoptotic signal starts from the cell-membrane
Andocs G, et al. Biology and Medicine 7(4):1-9, (2015)
Expression of: mHSP70, mHSP90, Trail-R2, CRT, Cyt-C, HMGB1
Andocs G, et al. Cell Stress and Chaperones 20(1):37-46, (2014)
Regulates different genes than the same temperature heating
Andocs G, et al. Cell Death Discovery (Nature Publishing Group), 2, 16039, (2016)
Produces immunogenic cell-death (ICD)
Vancsik T, et al. J. of Cancer, 20(1):37-46, (2018)
Forms APC with ICD process
Meggyeshazi N, et al. Hindawi, Conference Papers in Medicine, Volume 2013, Article ID 187835, (2013)

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

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

mEHT gains the local control and the survival simultaneously

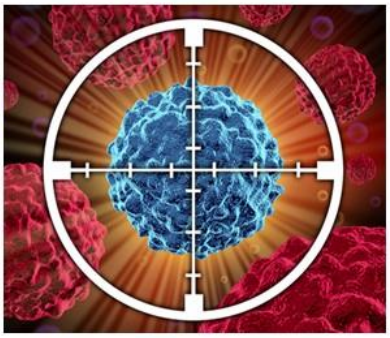
Clinical proofs for primary and metastatic malignancies (selected 21 from 100+ clinical)

Brain gliomas	1. Wismeth C, et al. J Neurooncol 98(3):395–405, (2010) 2. Fiorentini G, et al In Vivo 20(6A):721–724, (2006) 3. Roussakow S, BMJ Open, 7:e017387, (2017) 4. Hager ED, et al. Deutsche Zeitschrift für Onkologie 38(3):133-135, (2006) 5. Hager ED et al. J Clin Oncol, Ann.Meet.Proc.(ASCO Post-Meet.Ed.) 26:2047, (2008) 6. Sahinbas H, et al. Deutsche Zeitschrift fuer Onkologie 39:154–160, (2007)
Uterus cervix cancer	7. Lee S-Y, et al. Oncology Letters, DOI: 10.3892/ol.2017.6117(2017) 8. C Minnaar, et al. Physica Medica 32(2):151-152, (2016)
Pancreas cancer	9. Volovat C, et al. Romanian Reports in Physics 66(1):166-174, (2014) 10. Douwes FR, Biologische Medizin 35:126–130, (2006
Lung cancer	11. Ou J, et.al. European J Pharmaceutical Sciences, 109:412-418, (2017) 12. Lee DY, et al. Advances in Lung Cancer 4:1-7, (2015) 13. Lee DY, et al. Conference Papers in Medicine, Volume 2013, Article ID 910363, (2013)
Liver cancer	14. Hager ED. Deutsche Zeitschrift für Onkologie, 36:132-134, (2004) 15. Gadaleta-Caldarola G, et al. Oncol Lett, 2014 Oct,8(4):1783-1787, (2014)
Sarcoma	16. Jeung TS, et al. Case Reports in Clinical Medicine 4:157-168, (2015) 17. Volovat C, et al. Romanian Reports in Physics, 66(1):175-181, (2014)
Intraperitoneum	18. Pang CLK, et.al. Molecular and Clinical Oncology, 6:723-732 (2017)
Physiology	19. Lee S-Y, et al. Int J Hyp, 28:1-6'(2015) 20. Lee S-Y, et al. Int. J. Hyperthermia, online: 21 January, (2018)
Monotherapy	21. Jeung TS, et al. Conf. Papers in Medicine, Vol. 2013, Article ID 392480, (2013)

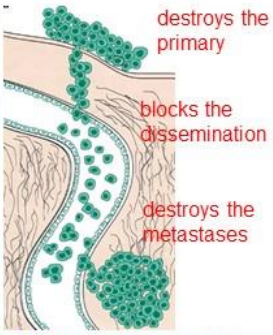
mEHT fits well to the modern oncology

Therapy targeting the malignant processes

Targeted therapy to malignant cells

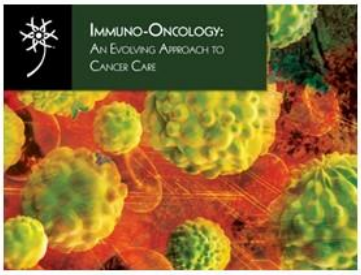


Complex therapy to system



ACTS SYSTEMICALLY

Direct and effective way to immuno-oncology



New kind of hyperthermia

- Heats selectively
- Physiology compatible
- Applicable dose
- Precise electronics

Thank you for your attention!

Acknowledgement

We would like to say thank you for the continuous help and support of the following institutes and people:

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Dr. Tibor Krenacs
Dr. Marwan Akasheh
Prof.Dr.Chang Geol Lee
Dr. Carrie Minnaar, …

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