電熱治療的作用與臨床療效

The Effects of Modulated Electro-hyperthermia and Clinical Outcome

曾 玉 華 醫師

Yuk-Wah Tsang M.D. Ph.D.

放射腫瘤科 /電熱治療中心

Dept. of Radiation Oncology

Electro-hyperthermia Treatment Center

05/09/2020

Outline

- Introduction of High temperature and fever range hyperthermia
- Deep regional hyperthermia vs Hyperthermic Intraperiotoneal chemotherapy (HIPEC)
- Features of modulated electro-hyperthermia (mEHT)
- Some clinical cases of mEHT
- Immunologic effects of mEHT
- Indications, duration, sequence and frequency of mEHT treatment
- Immunologic effects of mEHT
- Clinical outcome of hyperthermia and mEHT
- Summary

嘉基 G棟地下B2樓 放射腫瘤科





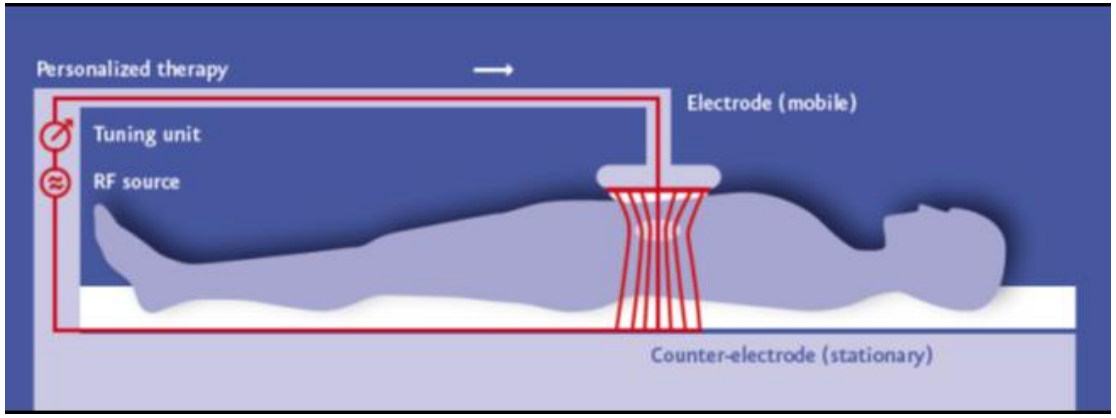
熱治療的分類

溫度	熱治療名稱	適應症	限制	腫瘤大小/治療泛圍	侵入性	合併治療
> 70°C	熱消融 (射頻)	肝腫瘤 神經阻斷	血管旁 器官邊緣	<3公分 一次治療	需定位 針刺	無
> 50°C	海扶刀 (超音波)	子宮肌瘤 骨轉移	空氣及骨骼無法穿透 超音波影像必須良好	一次治療一個點，累積治療一個體積	需麻醉	無
40°C~44°C	熱治療					
	BSD	多為骨盆腔腫瘤	空氣邊 易過熱	15公分 骨盆腔內 多次治療	無	需合併治療
	RF-8	腦部以下腫瘤皆可	脂肪易過熱	30公分內 可多次治療	無	需合併治療
	Oncothermia	腦部及全身腫瘤皆可	無	30公分內 可多次治療	無	需合併治療
< 40°C	遠紅外線	保養為目的 癌症效果不佳	不易升溫	全身	無	需合併治療

電熱療(mEHT)與溫熱化療(HIPEC)是不同的東西!

Non-invasive





Modulated Electro-hyperthermia (mEHT) / Oncothermia source: google.com

Invasive !

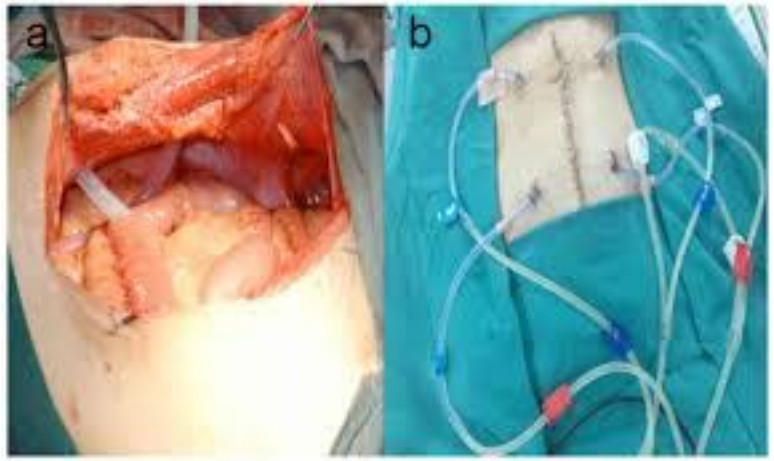
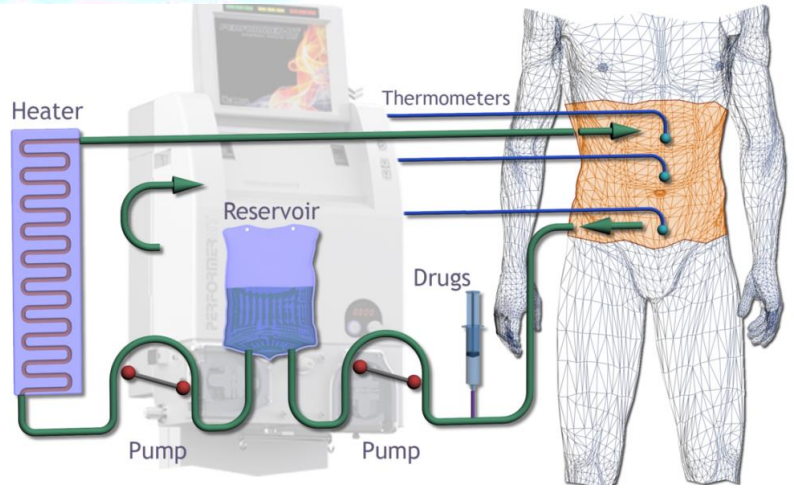



Figure 7. HIPEC application with closed abdominal technique



Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) Source: google.com

熱治療機

1. 微波熱治療機 BSD-2000



2. 安可勝電熱治療機 Oncotherm

Modulated Electro-hyperthermia (mEHT)

or ONCOTHERMIA



3. 射頻熱治療機 RF-8

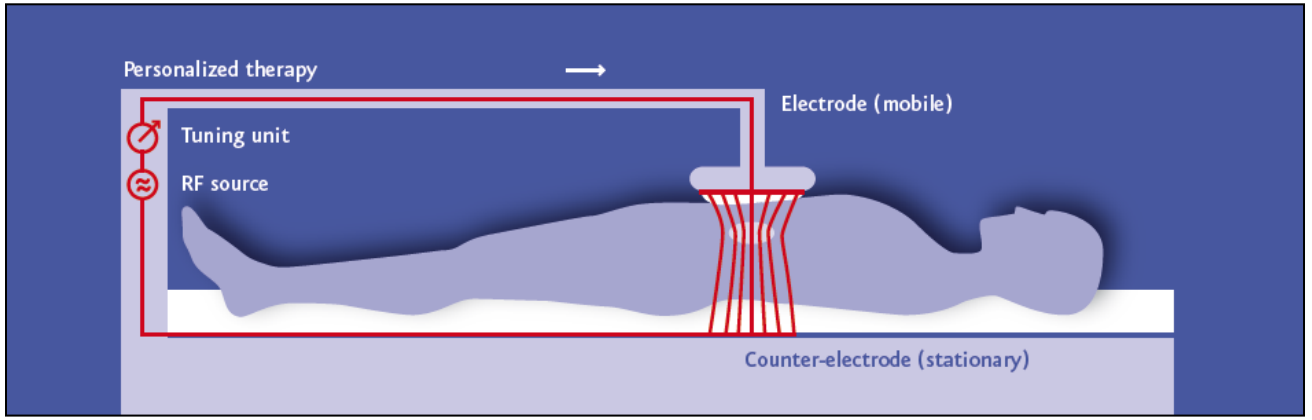


4. Celsius 42℃



Pictures source: google.com

電熱療的簡單理論



病人與腫瘤形成一個電迴路

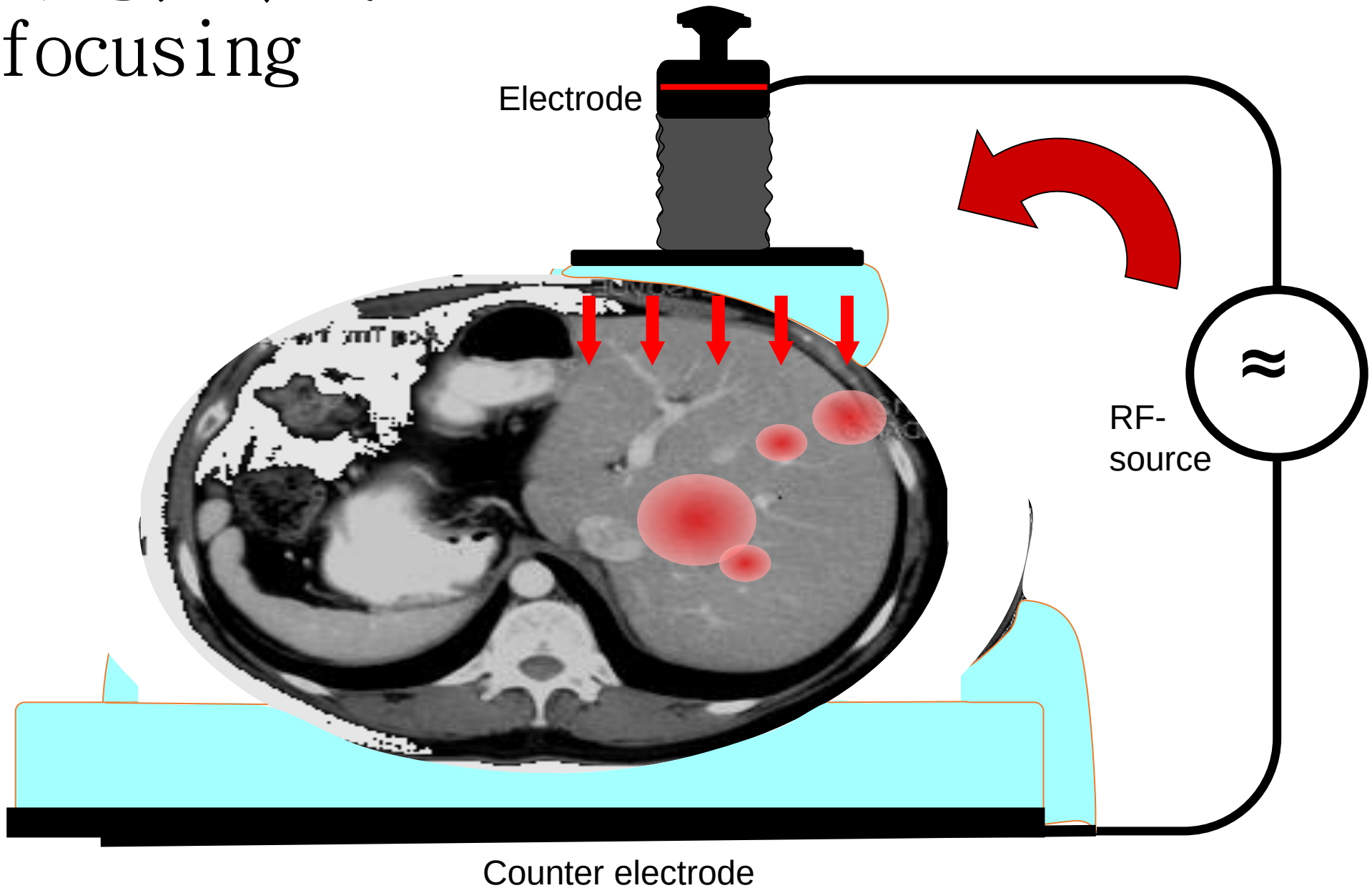
1. Heating (加熱)
2. Autofocusing (自動對焦)
3. Frequency modulation

(頻率調變)

Unique features of

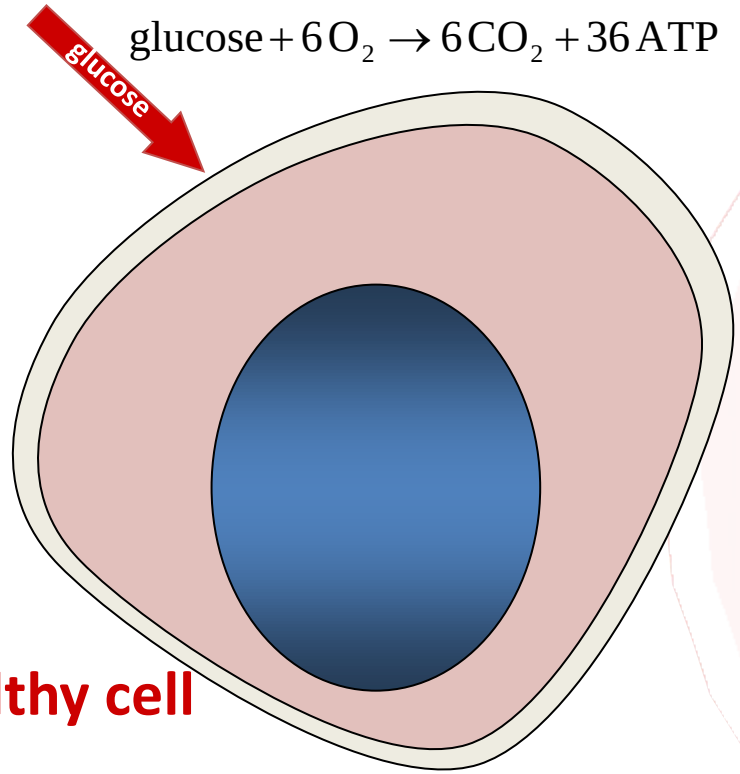
專利特色

安可勝電熱療機
Autofocusing



細微觀：細胞的代謝

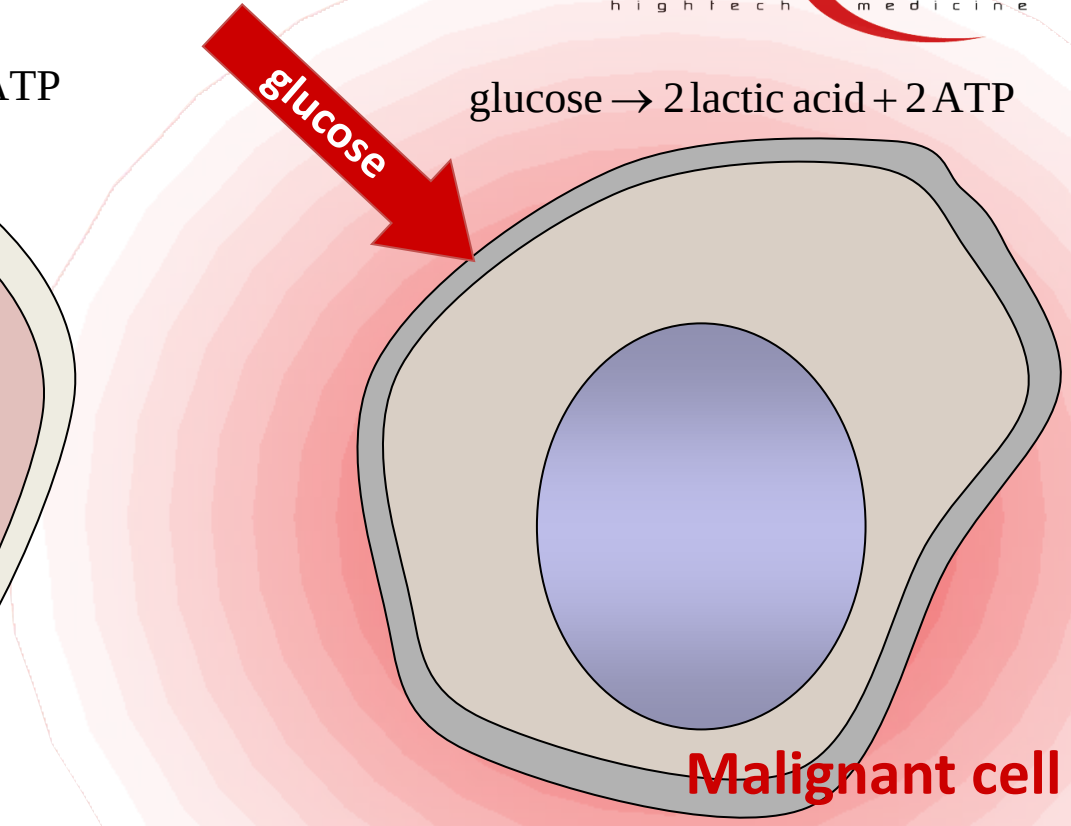
Cellular difference



$$\text{glucose} + 6\,O_2 \rightarrow 6\,CO_2 + 36\,\text{ATP}$$

Healthy cell

- Low glucose influx
- Normal ECM
- High membrane potential
- Strong connection to next cells
- Texture order
- Collectivity
- Served by the collective



$$\text{glucose} \rightarrow 2\,\text{lactic acid} + 2\,\text{ATP}$$

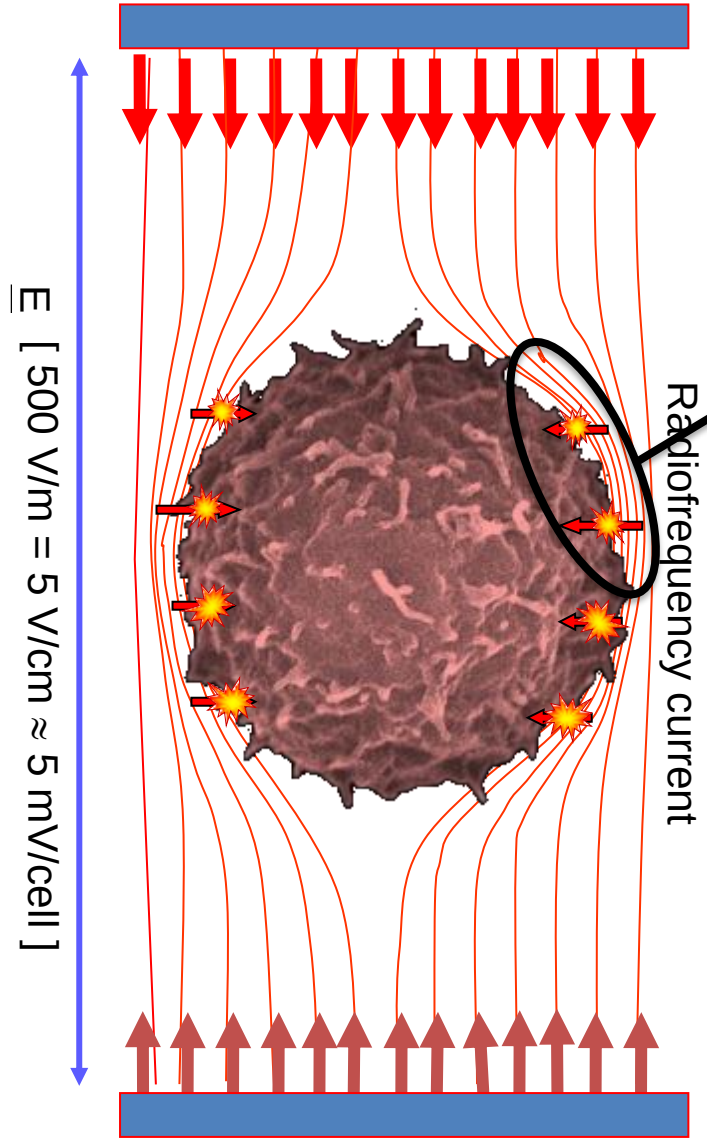
Malignant cell

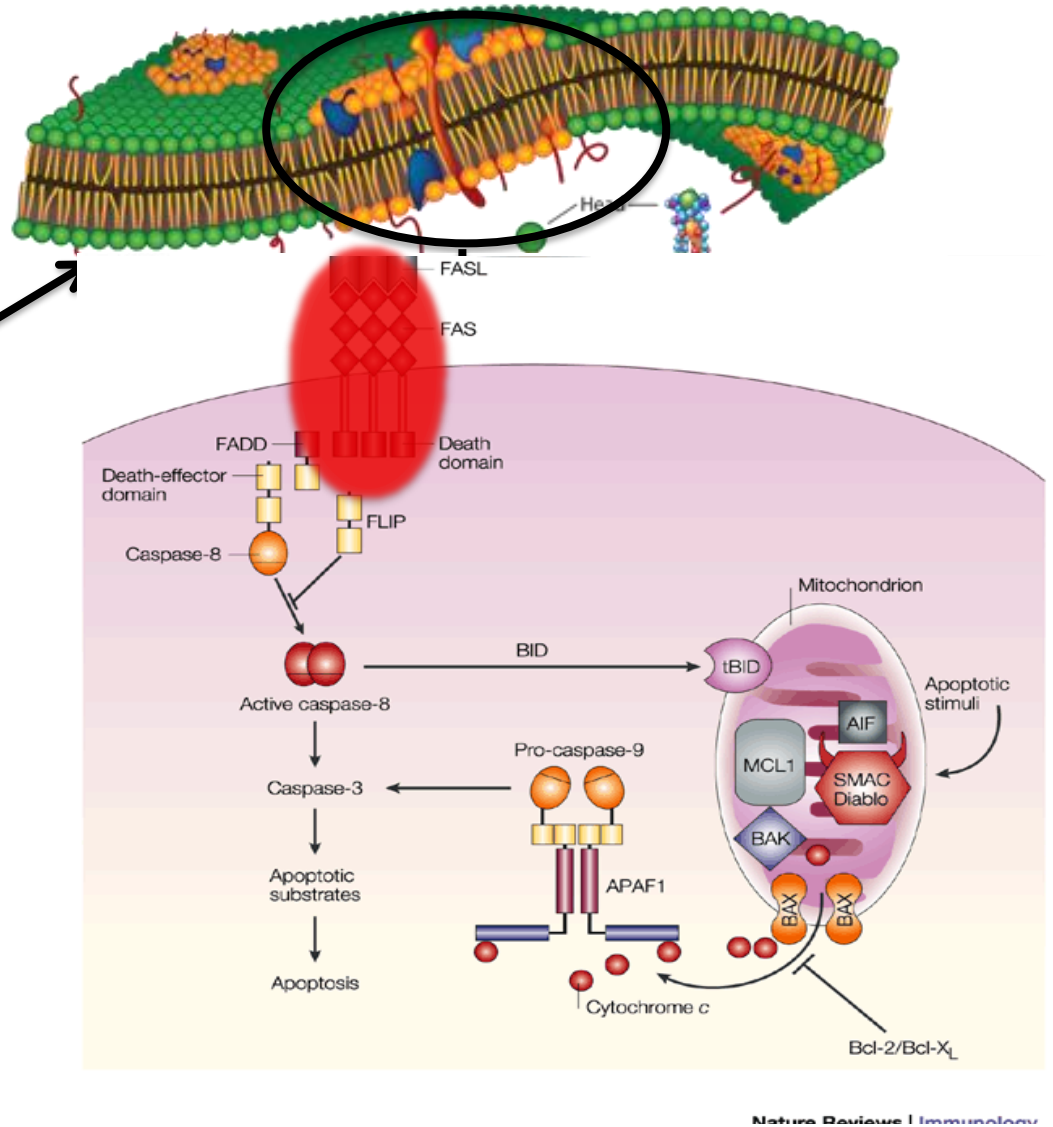
- High glucose influx
- High ion-concentration in ECM
- Low membrane potential
- Lazy connection to next cells
- Disorder
- Autonomy
- Fighting with all others

Consequence: the malignant cell are distinguishable by their biophysical parameters

The nanoheating concept of the oncothermia method

The nanoheating concept of the oncothermia treatment is a well elaborated theoretical framework

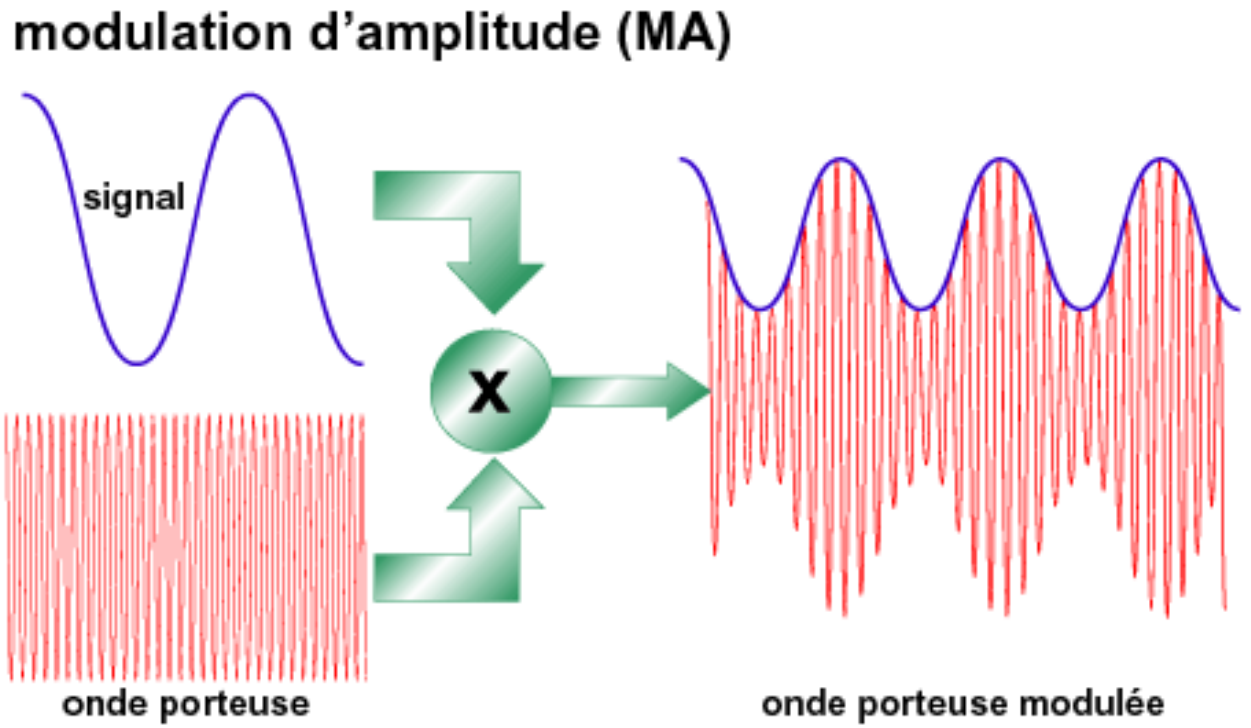




The heat-stressed membrane rafts initialize signal transduction pathways from the membrane!

調變（modulation）

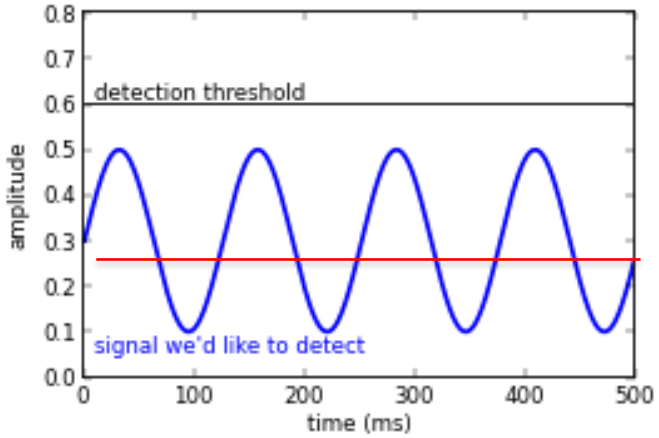
- 調變是一種將一個或多個週期性的載波混入想傳送之訊號的技術

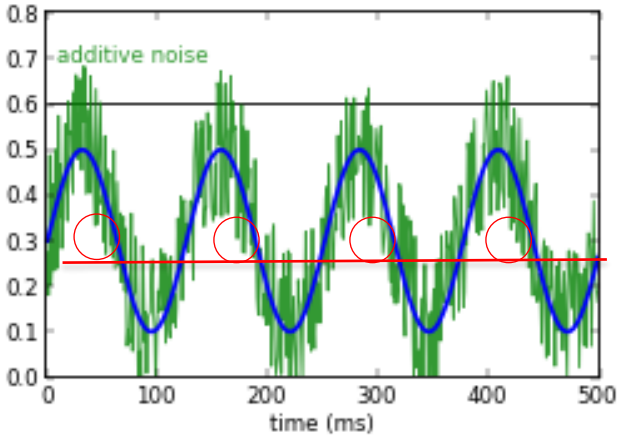


Carrier wave

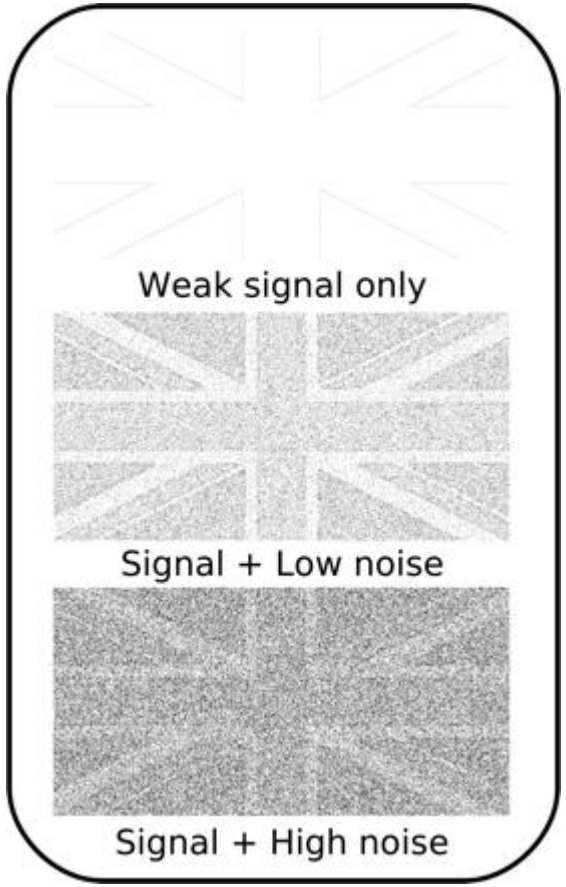
隨機共振 (stochastic resonance)

- Stochastic resonance (SR) is a phenomenon where a signal that is normally too weak to be detected by a sensor, can be boosted by adding white noise to the signal, which contains a wide spectrum of frequencies.









先看看這些案例！

Chemo
MMC+5FU x6
Cisplatin + 5FU x2
Oncothermia

Tonsils carcinoma

Investigator: Prof.Dr. A. Herzog;
Institute: Fachklinik Dr.Herzog, Nidda, (Bad Salzhausen), Germany;

Patient: 55 y, female (H.M.);

Diagnosis: Tonsils carcinoma, (squamous), lymph and pulmonary metastases

Treatment: Oncothermia & chemotherapy; (6x Mitomycin und 5-FU, 2x Cisplatin/ 5FU)

Results: partial remission, symptoms disappeared, no complains

Before therapy (May, 2009)

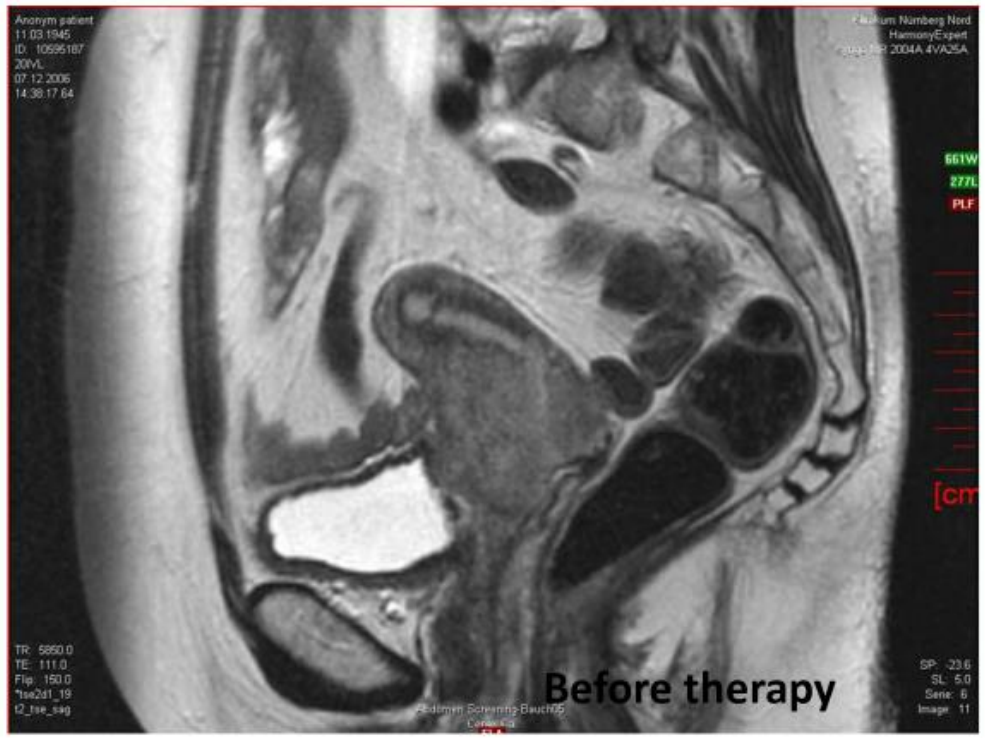


After 8 cycles of therapy (February 2010)



Cervix carcinoma

Investigator: Prof. H. Renner
Department: Klinikum Nord, Nürnberg, Germany
Patient H.K, 61 y, female; Cervix carcinoma; cT4 cN0 M0 G3
Histology: Squamous cell carcinoma;
Therapy: 12/06-01/07 bimodality therapy, Radiotherapy: 50.4 Gy; (5x1.8 Gy/weeks); oncothermia: 6 sessions.
Control: 3 months later hysterectomy (Wertheim).
Result: pathologically complete remission ypT0ypN0



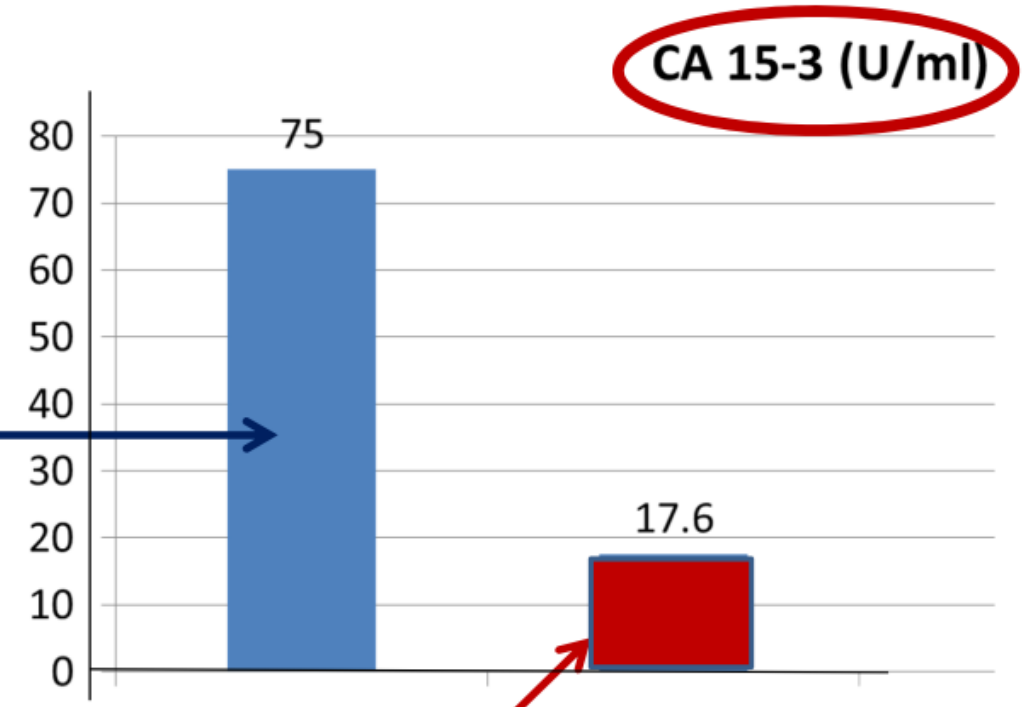


Mammary carcinoma with liver metastasis

Investigators: Dr. W-P. Brockmann **Institute:** Dr. W-P. Brockmann Institute OncoLight, Hamburg, Germany.
Patient: 58 y**,** female. **Primery-tumor:** Mammary CA with liver metastasis, diagnosed;
Treatment: Radiotherapy, whole-body hyperthermia, oncothermia, and local dendritic cell therapy
Result: partial remission





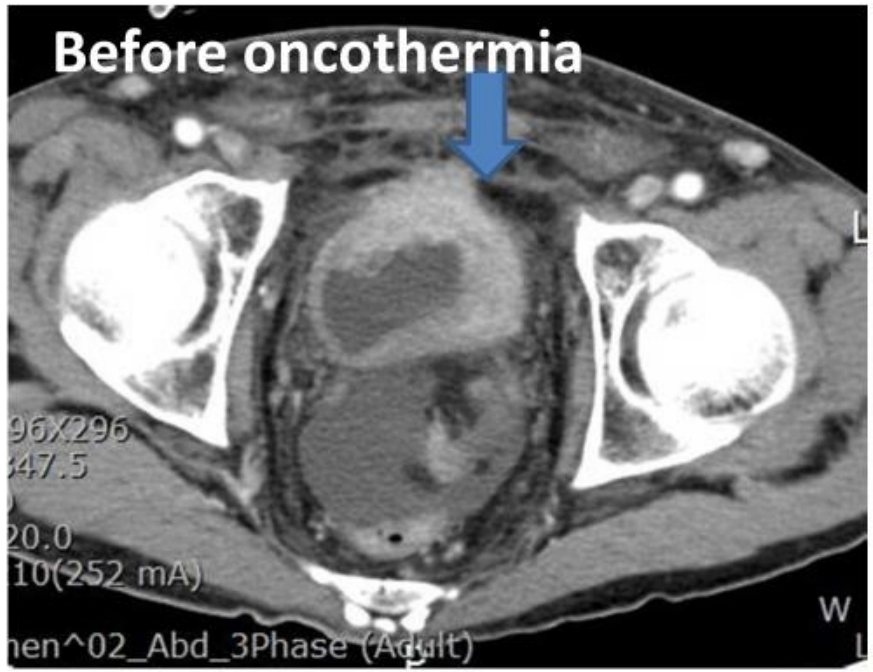


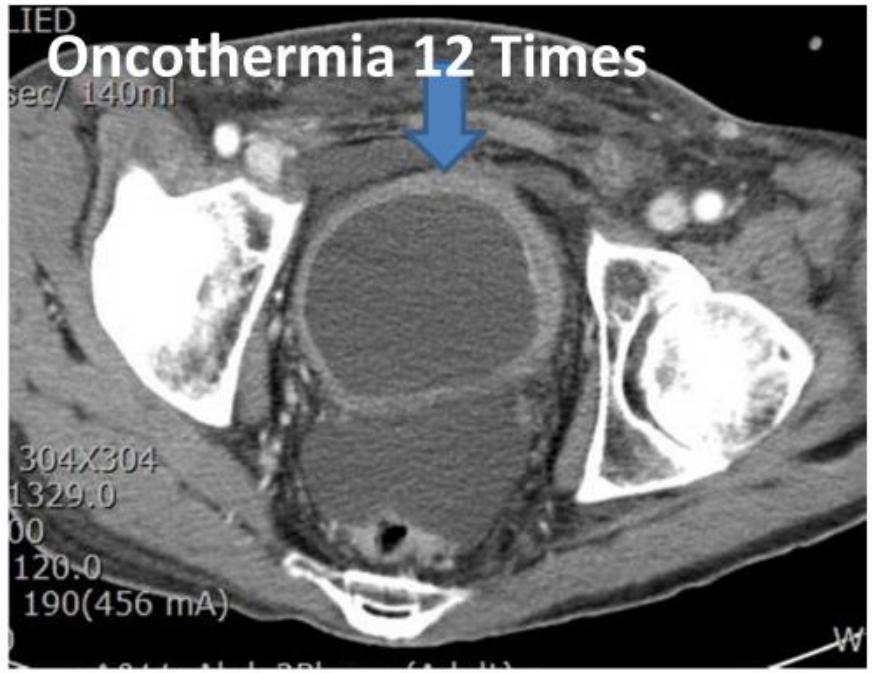




Pancreatic Ca and Metastatic Bladder Cancer (49y/M)

Investigator: Prof.Dr.Taesing Jeung
Institute: Department of Radiotion Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital.
Oncothermia applied as monotherapy
Published: 31st ICHO Oct. Budapest; 2012

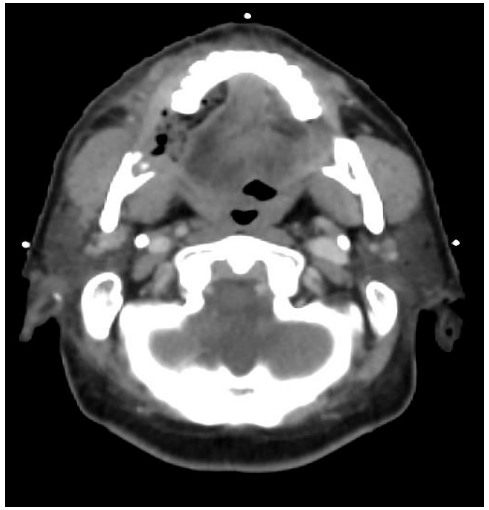
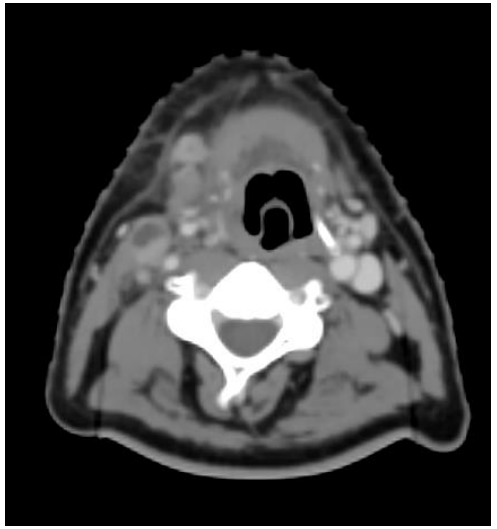




58y/o male, R't side lower gingivobuccal mucosal SCC, cT4bN2bM0 s/p induction C/T and CCRT 70Gy with complete response (CR), biopsy after 8 weeks: negative

治療前



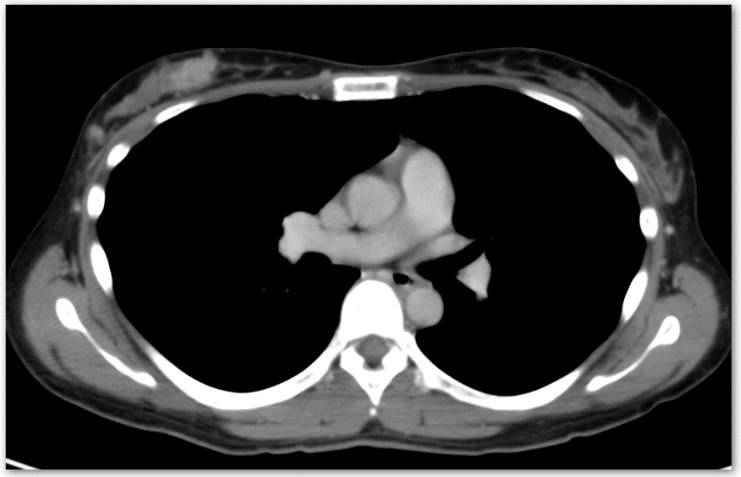
治療後:

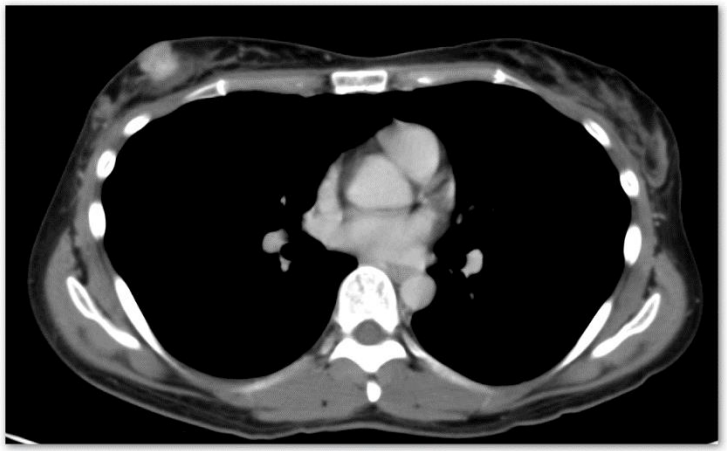
RT 70Gy/35次
+
Oncothermia
x 8次




41 y/o lady, right breast, Invasive Ductal Carcinoma

治療前





Multiple Rt breast nodules, largest over UOQ(>2.5cm).ie cT2(m) (but tiny subcutaneous nodules may suggest skin spread r/o cT4a)

- cT4aN1M1 stage IV with lung metastasis s/p palliative bio-C/T TC regimen x 1(1081112) then TPH regimen x 7(1081203-1090416) followed by PH regimen x 1(1090507), then right nipple sparing simple mastectomy + mEHT x 8 sessions
- SM+SLND+DIEP(1090521)，ypT1cN0M1

38 y/o man, sqcc of esophagus, cT3N3M0

治療前





治療後

CCRT 3780cGy/21fx +
mEHT x 8 sessions → op



病理:

Microscopic Finding

It reveals a picture of esophageal tumor, featured by:
1. Tumor type: Squamous cell carcinoma
2. Histological grade: Moderately differentiated
3. Lymphovascular invasion: Absent
4. Perineural invasion: Absent
5. Tumor extension: Tumor invades adventitia (section A3)
6. Proximal and distal surgical ends: Free of tumor cells
7. Circumferential margin: Free of tumor cells, 1mm.
8. Stomach: Negative for tumor involvement.
9. Lymph nodes: Negative for metastatic carcinoma. (perigastric: 0/2; mediastinal: 0/33)
10. Tumor regression grade after preoperative chemoradiotherapy (Mandard, Cancer 1994)
    [ ] Grade 1 Complete regression: absence of histologically identifiable residual cancer; fibrosis extending through the wall; keratin plugs or neoplastic squamous ghost cells scattered in dense fibrosis of lymph node(s)
    [ ] Grade 2 Presence of rare residual cancer cells scattered through fibrosis
    [*] Grade 3 Increase in the number of residual cancer cells, but fibrosis still predominates
    [ ] Grade 4 Residual cancer outgrowing fibrosis
    [ ] Grade 5 Absence of regressive changes
11. Three-tiered grading system advocated by Wu TT, et al., Am J Surg Pathol 2007.
    [ ] P0, 0% residual tumor
    [*] P1, 1%-50% residual tumor
    [ ] P2, >50% residual tumor

All of 33 dissected lymph nodes reveal reactive hyperplasia without evidence of metastatic carcinoma. The distribution
is as follows: upper paraesophageal: 0/6; right RLN: 0/2; group 2L: 0/0; group 2R: 0/6; group 4R: 0/10; celiac LN: 0/6;
group 7: 0/3.

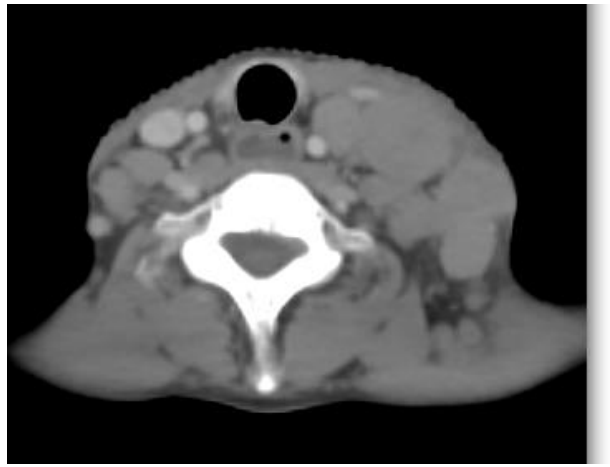
45 y/o man, small cell ca. of esophagus, multiple mets, cT4N3M1

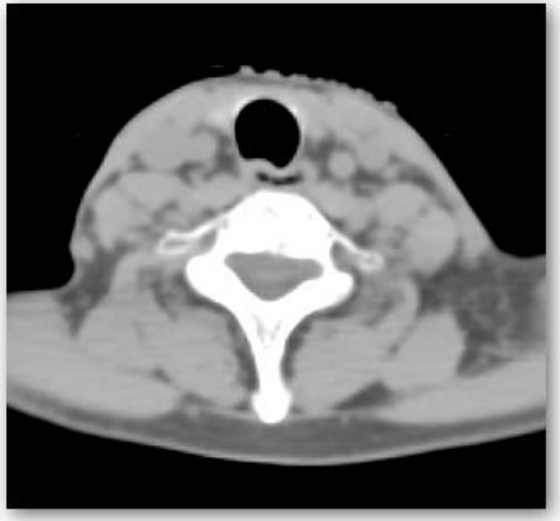
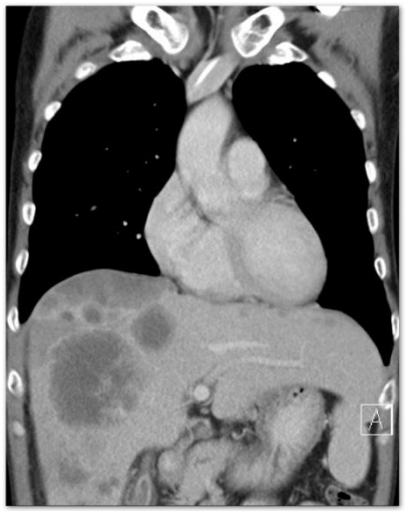
治療前

Oncothermia x 8
Esophageal tumor + neck LAP 35Gy/14fx

Liver mets and LAP RT 24Gy/12fx

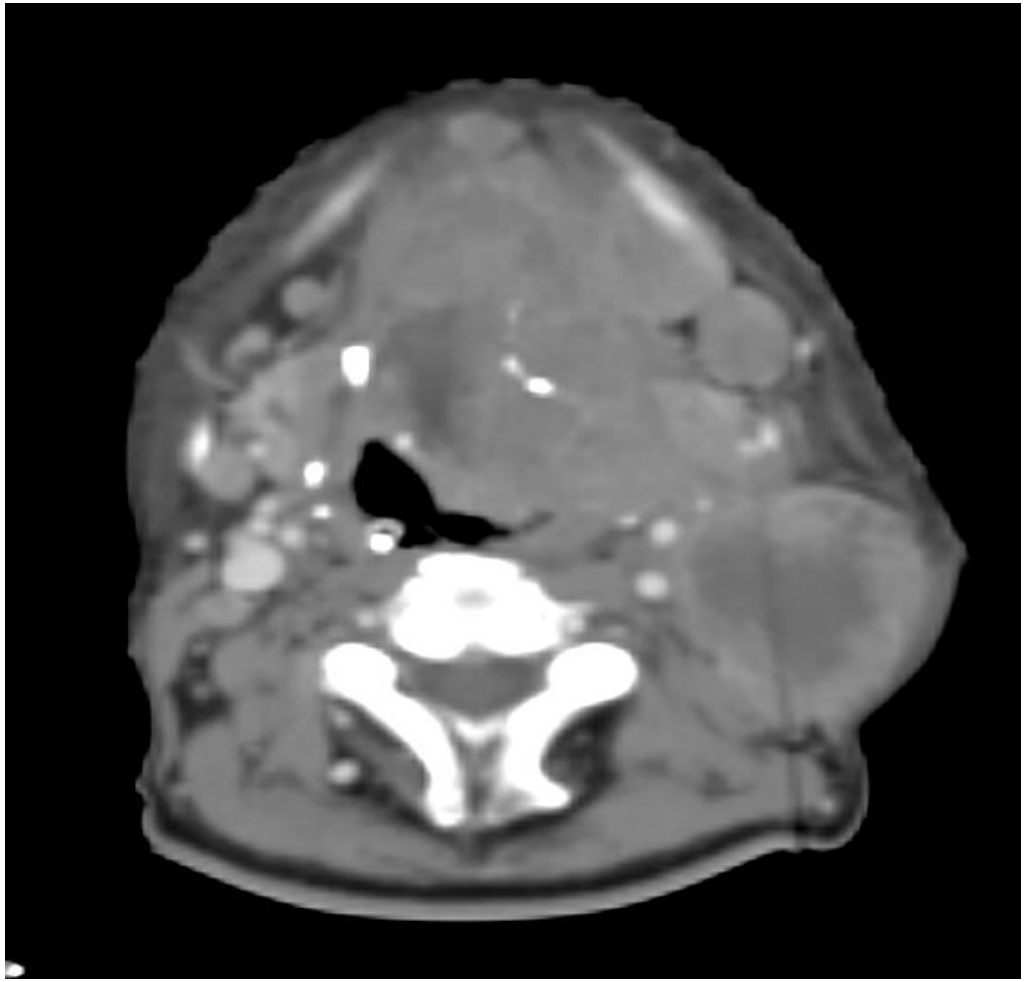
治療後

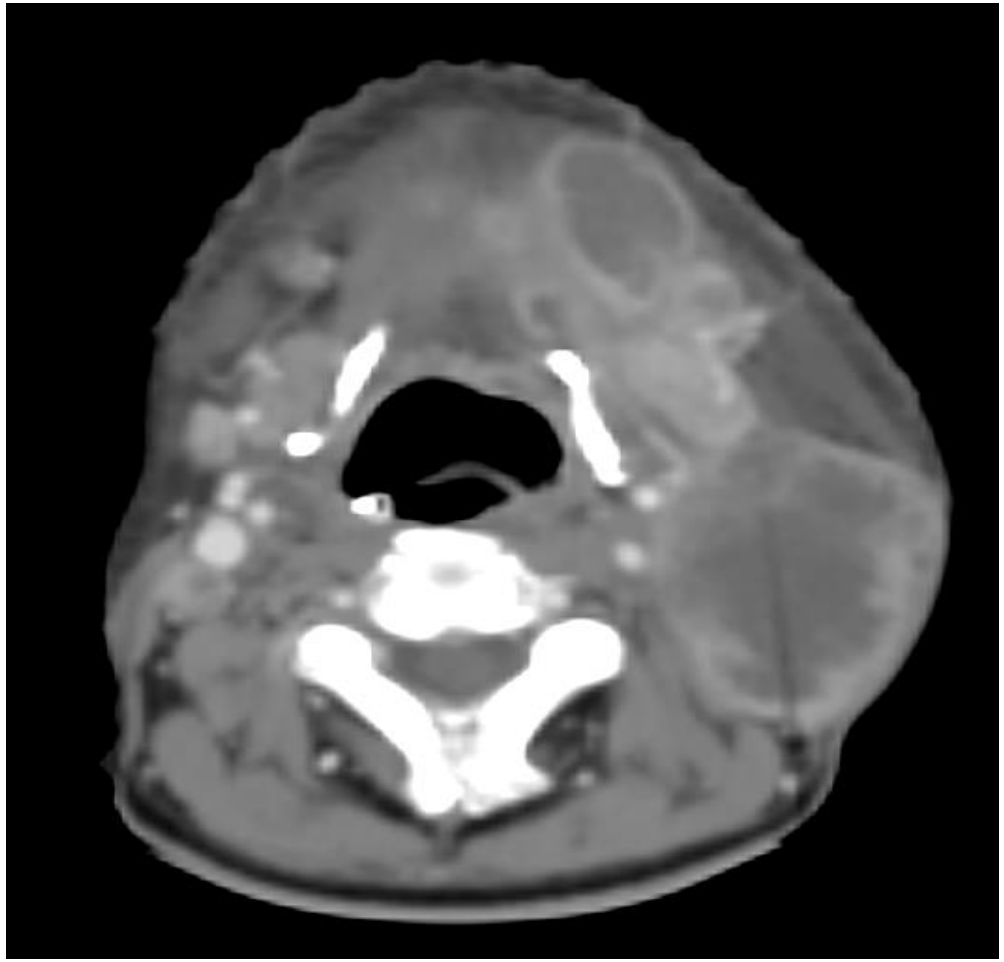




腫瘤壞死缺氧、血流不通對放療或化療不敏感

Before Treatment 放療前

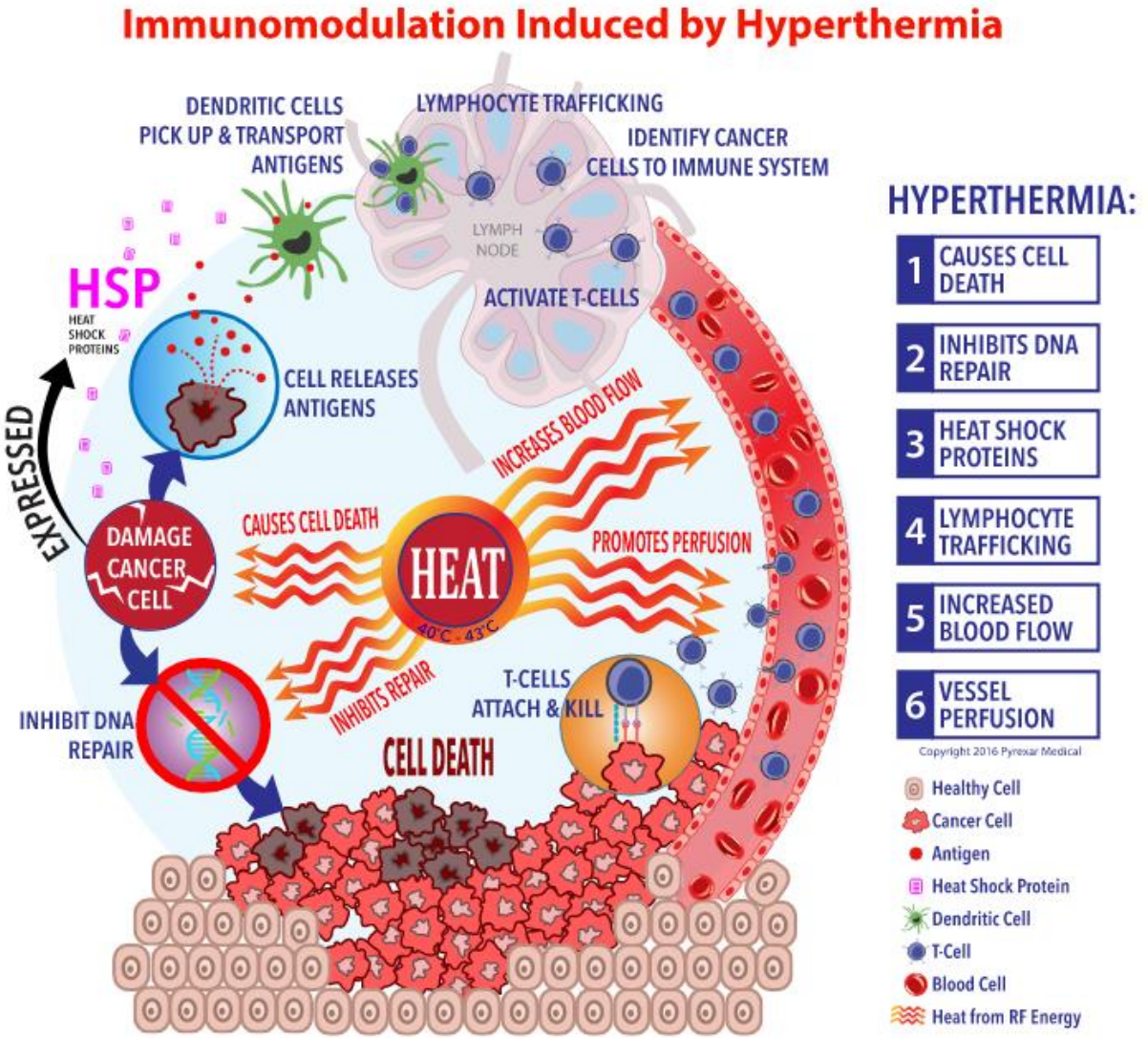


Near the end of Treatment 放療快結束時



熱治療的功效

- 改善腫瘤血流、缺氧→加強化療、放療、化放療、免疫治療的功效
- 抑制癌細胞的DNA修復，癌細胞容易凋亡
- 改善腫瘤微環境(micro-environment)，透過熱休克蛋白(HSP70)誘發身體免疫力以打擊癌細胞
- 熱療單用效果不如合併放療、化療和免疫治療，但有些 case 仍有驚喜，一般不能再放療、化療的病患才考慮單用熱療



Source: google.com

電熱療加上精準直線加速器效果將不輸昂貴的重離子機

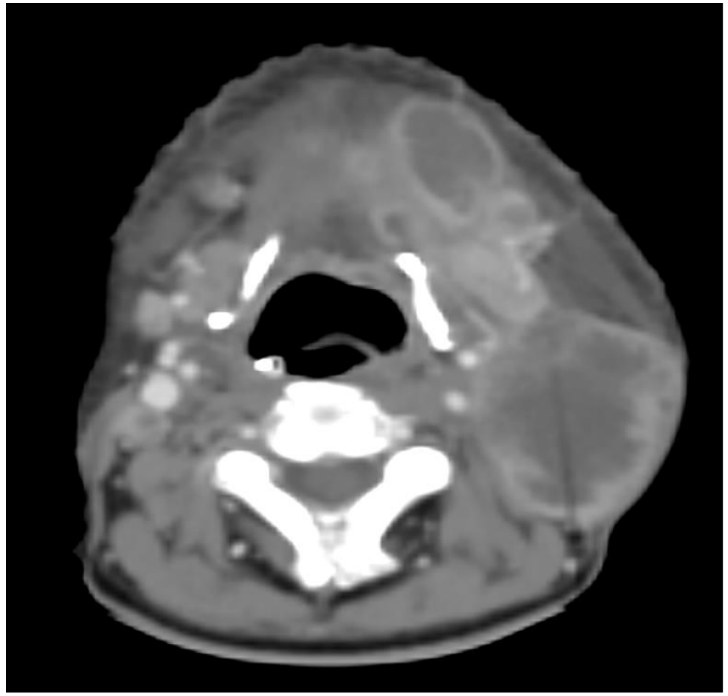
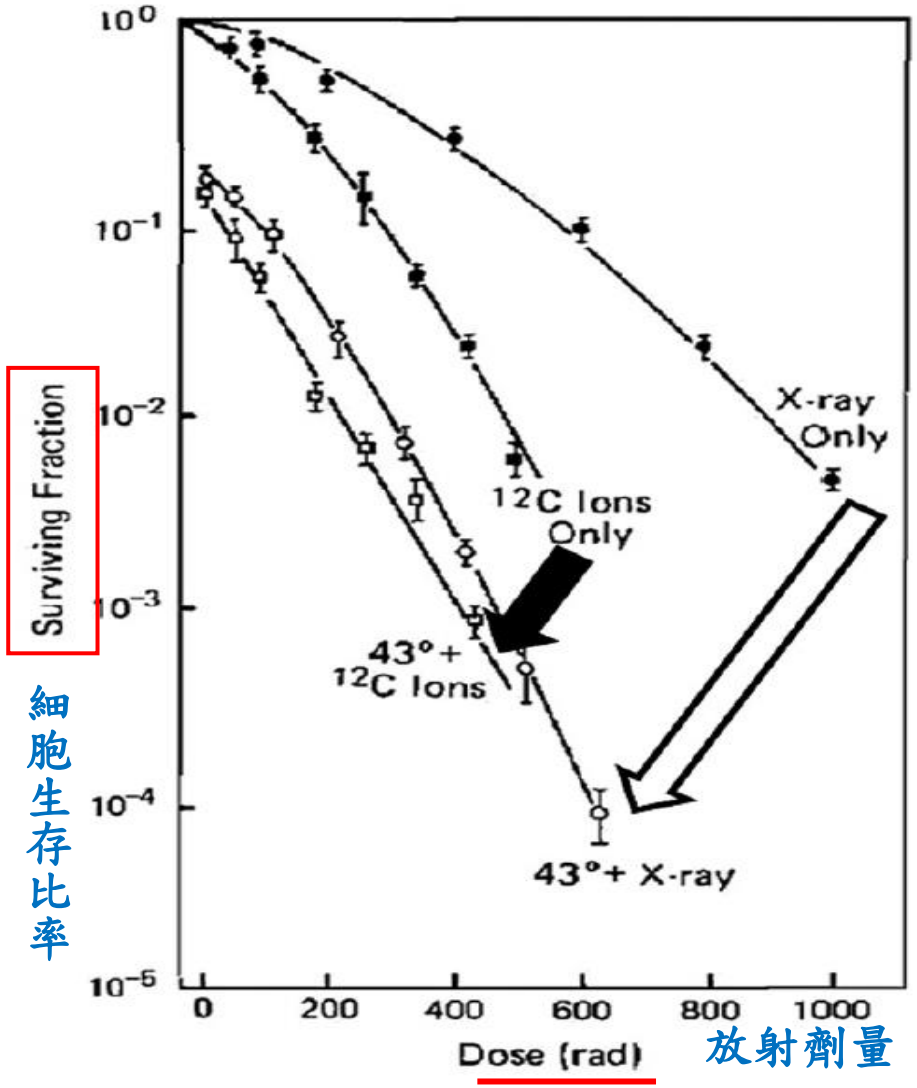


Figure 2. Survival of asynchronous CHO cells exposed to either 4 MeV X-rays (circles) or ^{12}C ions (squares) either at 37 °C (filled circles and squares) or 43 °C (open circles and squares). The marked thermal sensitisation at 43 °C is evident with X-rays while it was minimal with ^{12}C ions (black arrow). Reproduced with permission [49].



Int J Hyperthermia, 2014; 30(7): 524–530

Immunologic effects of Oncothermia (mEHT)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

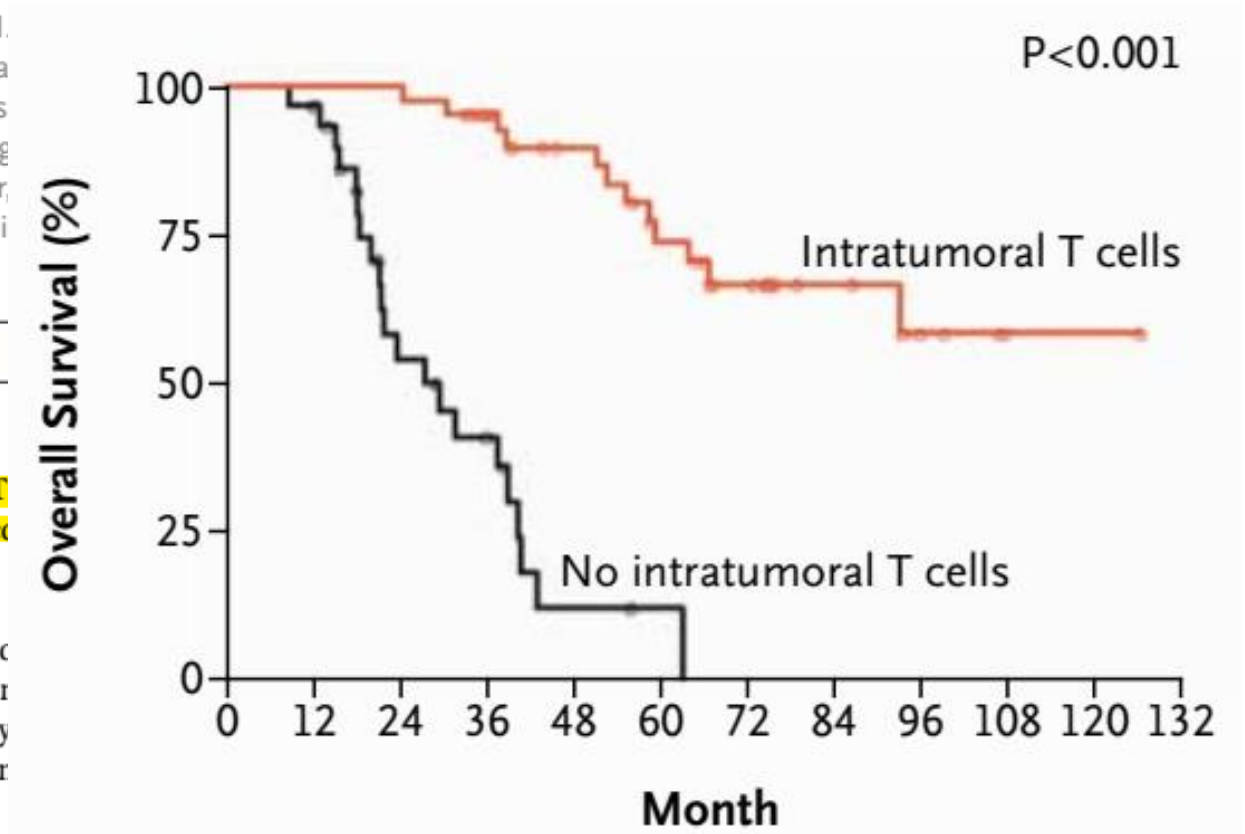
Lin Zhang, M.
Dionyssios Katsa
Marco Mas
Antonis Makrig
Katia Schlienger,
Stephen C. Rubi

BACKGROUND

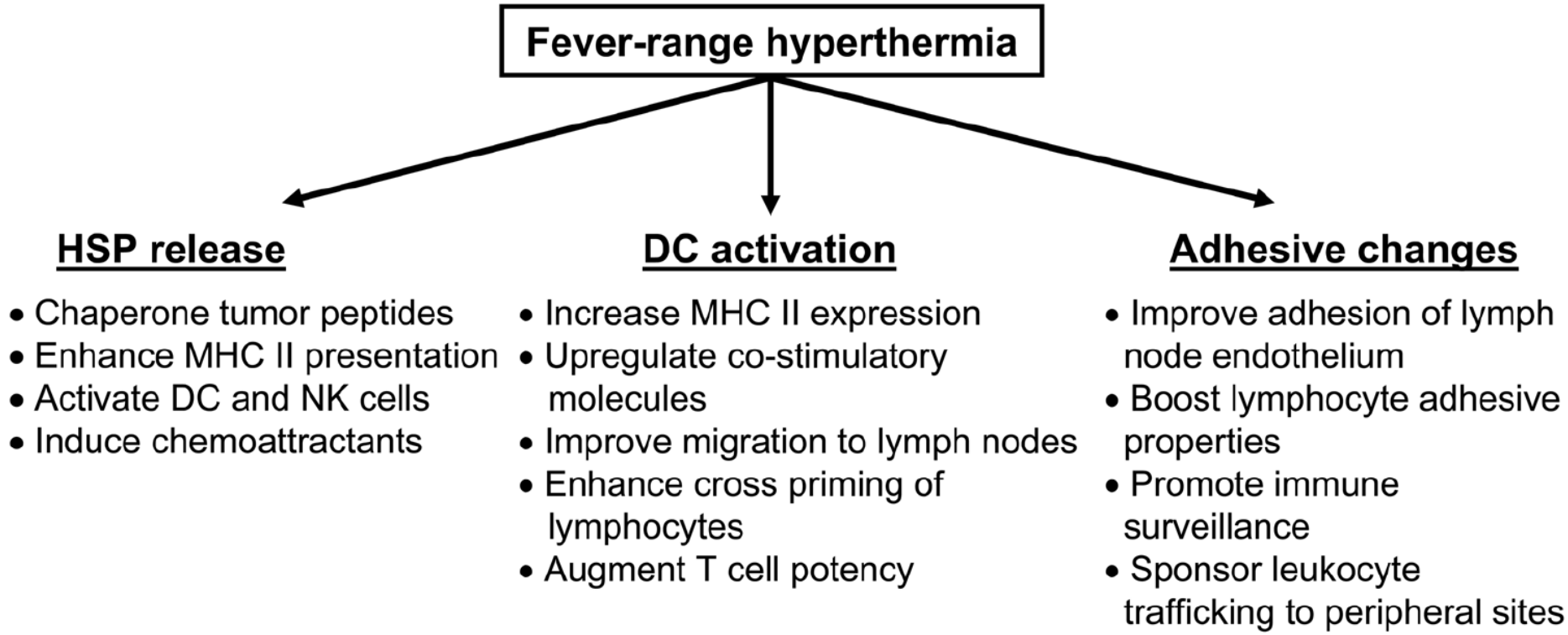
Although tumor-infiltrating T
association with clinical outc

METHODS

We performed immunohistc
vanced-stage ovarian carcinor
and conducted outcome analy
by real-time polymerase chair



N Engl J Med. 2003 Jan 16;348(3):203-13.



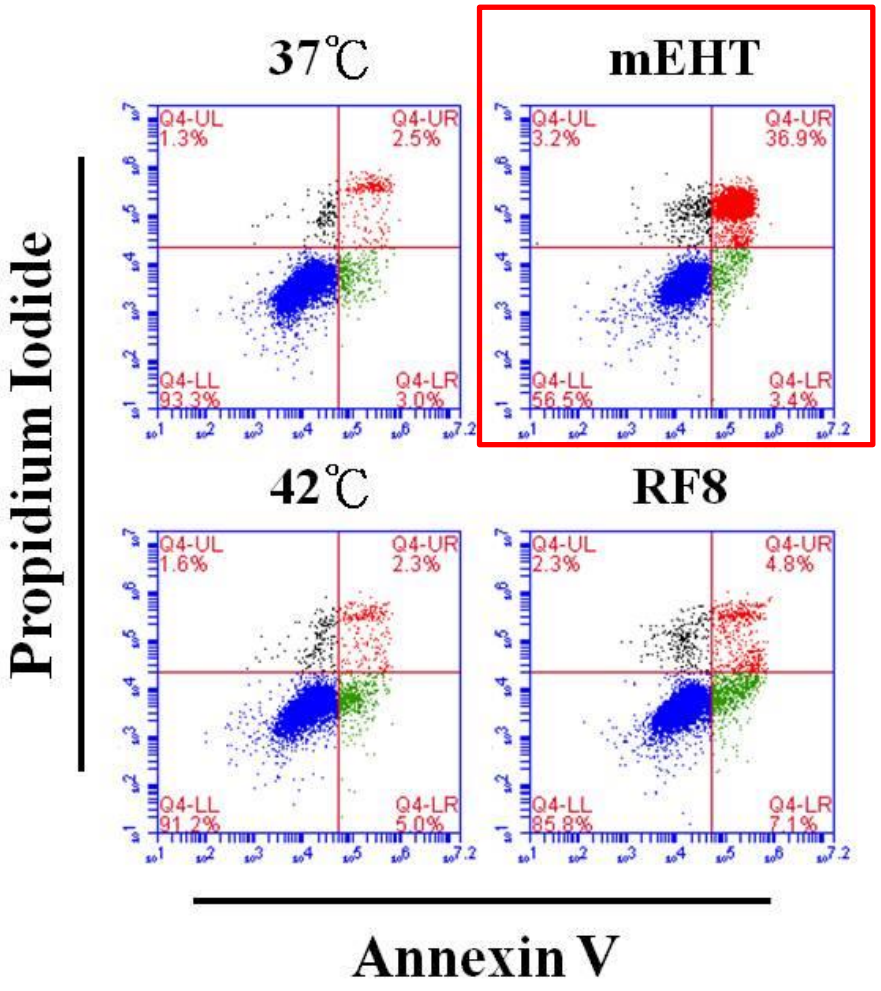
Curr Opin Investig Drugs. 2009; 10: 550–558.

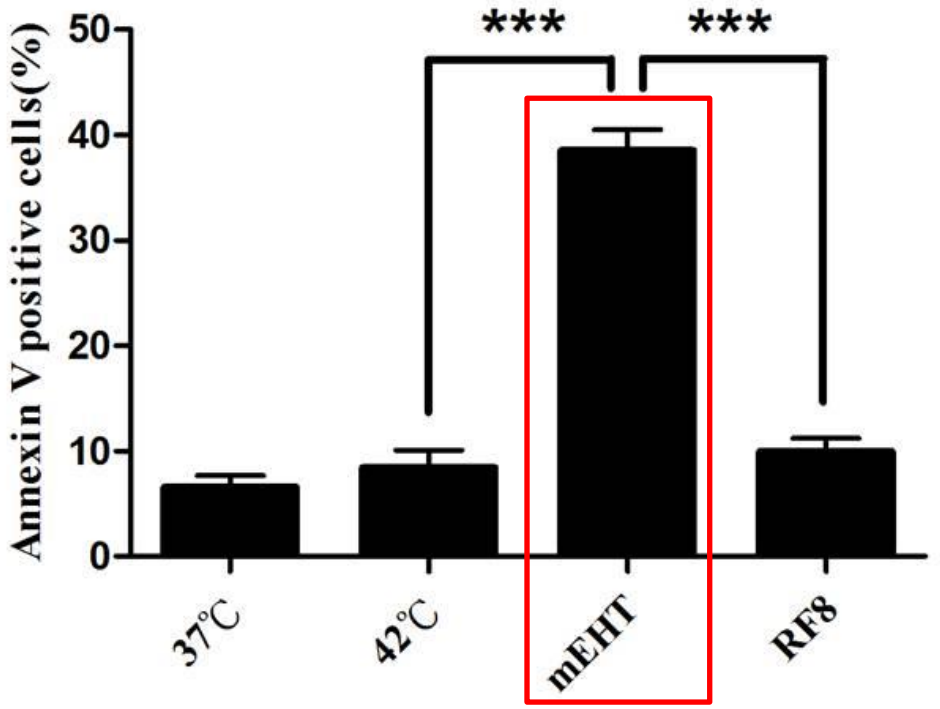
Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

Significant Elevation of Apoptosis After Modulated-Electro-Hyperthermia (mEHT) Treatment

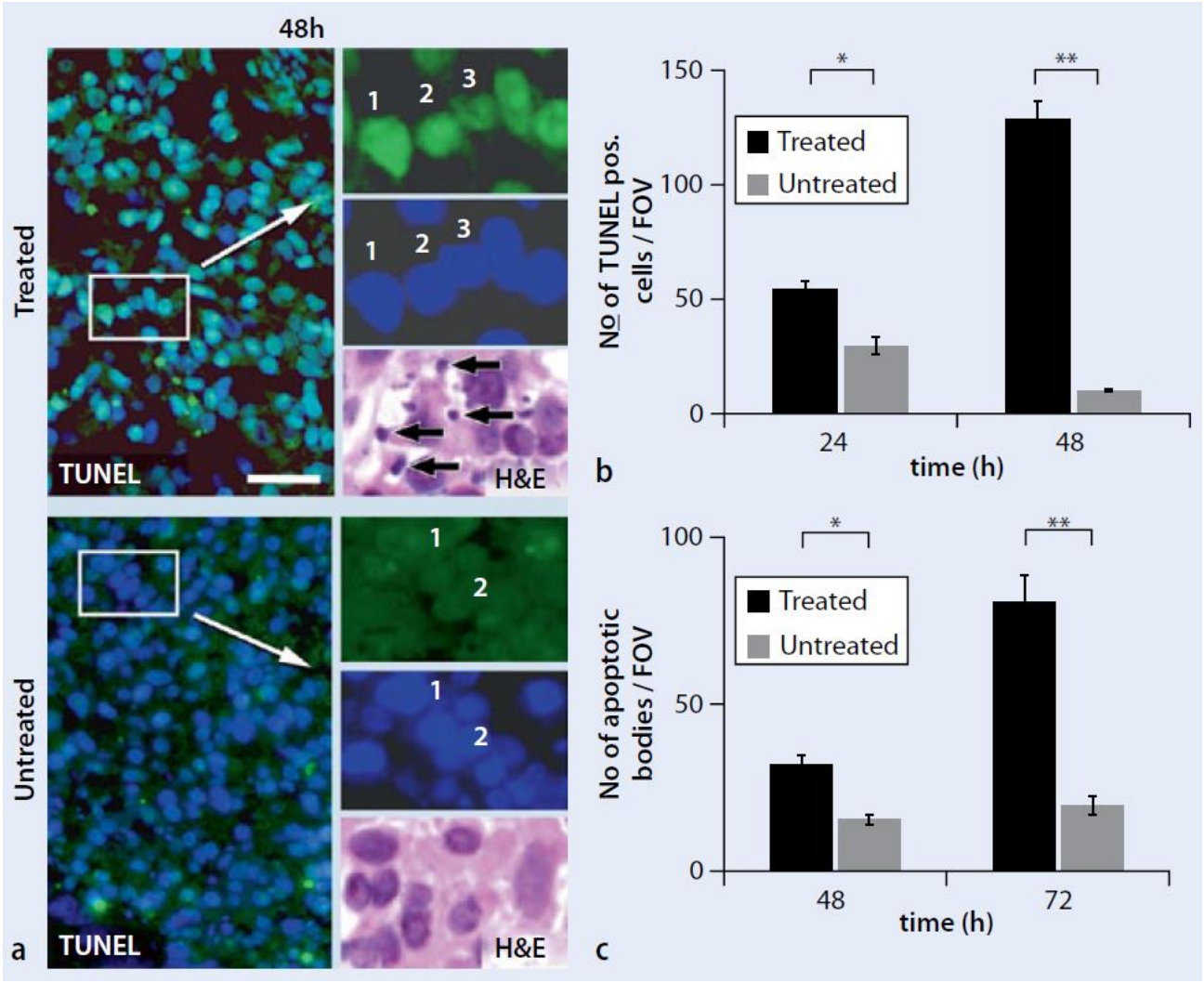




42˚C: Water Bath Control
RF-8: Conventional Hyperthermia

Yang KL et al, Oncotarget. 2016;7(51):84082-84092.

Significant Elevation of Apoptosis After Oncothermia Treatment



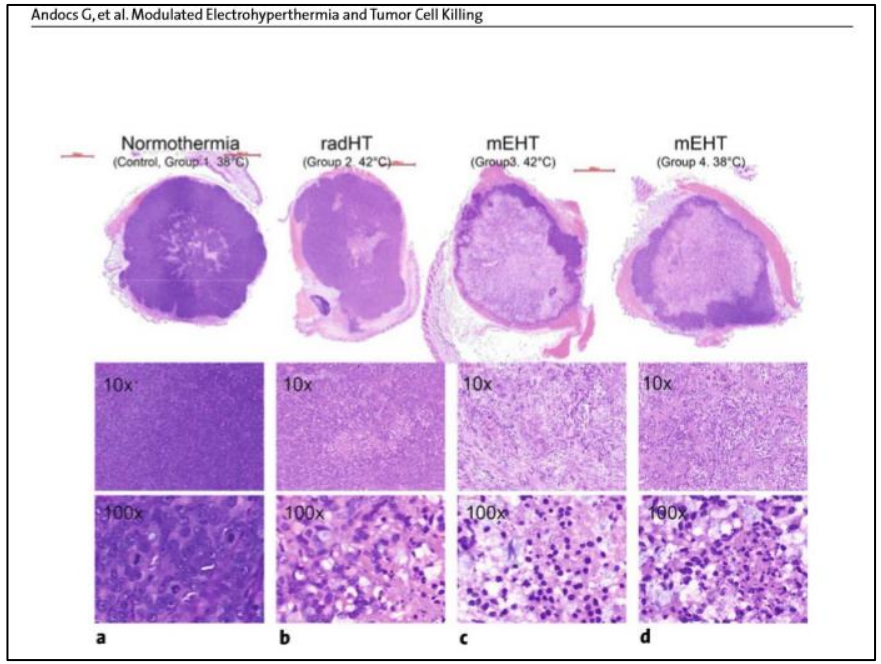
Meggyeshazi N et al, Strahlenther Onkol 2014; 190:815-22.

Strahlentherapie
und Onkologie

Original Article

Strong Synergy of Heat and Modulated Electromagnetic Field in Tumor Cell Killing

Gabor Andocs[1,2], Helmut Renner[3], Lajos Balogh[1], Laszlo Fonyad[4], Csaba Jakab[5], Andras Szasz[6]



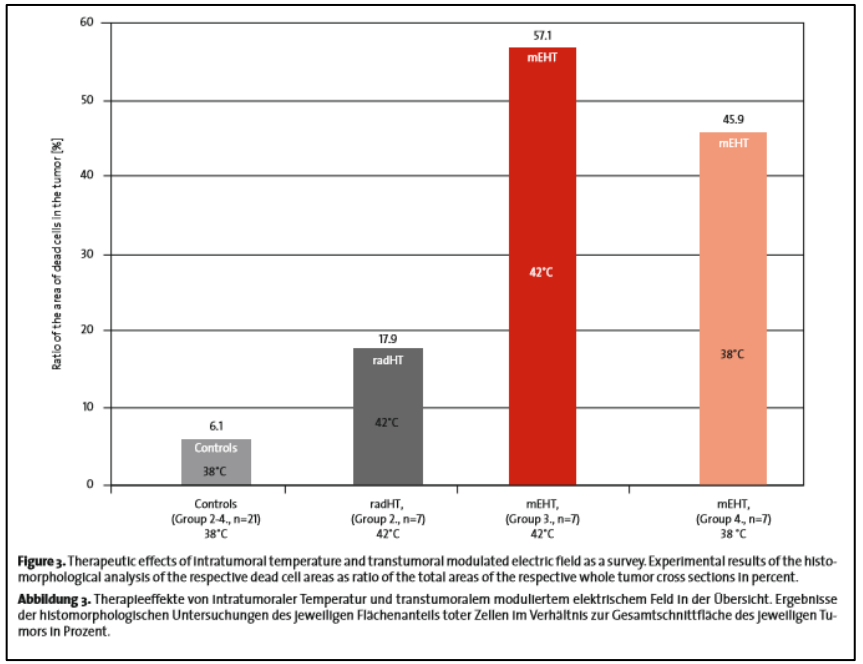


Figure 3. Therapeutic effects of intratumoral temperature and transtumoral modulated electric field as a survey. Experimental results of the histomorphological analysis of the respective dead cell areas as ratio of the total areas of the respective whole tumor cross sections in percent.

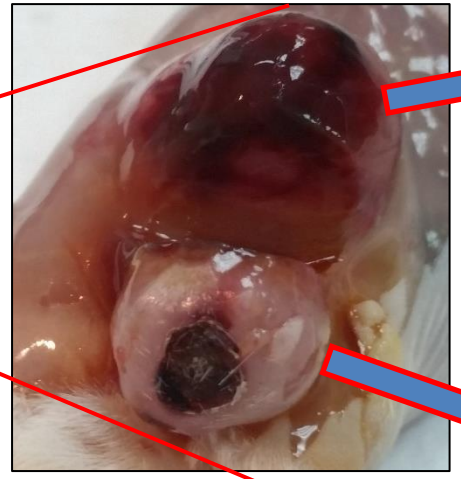
Abbildung 3. Therapieeffekte von intratumoraler Temperatur und transtumoralem moduliertem elektrischem Feld in der Übersicht. Ergebnisse der histomorphologischen Untersuchungen des jeweiligen Flächenanteils toter Zellen im Verhältnis zur Gesamtschnittfläche des jeweiligen Tumors in Prozent.

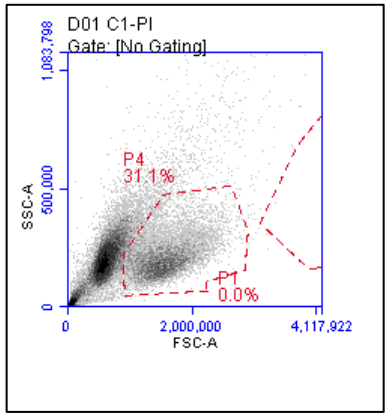
G. Andocs, Strahlenther Onkol 2009; 185: 120-6

Tumor Cell Death Analysis After mEHT Treatment

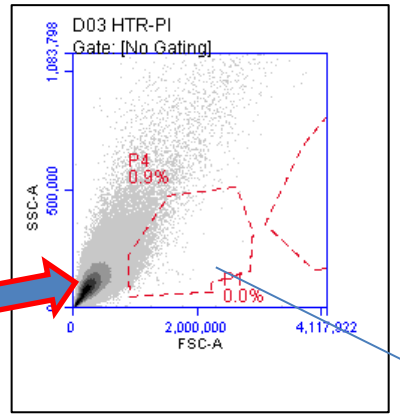
48h after treatment





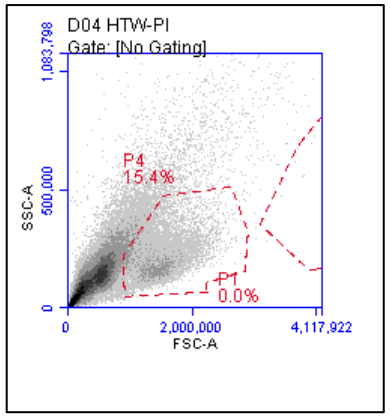


Untreated Control
Single Tumor



mEHT Treated
Death Area

Live tumor cells



mEHT Treated
Original Area

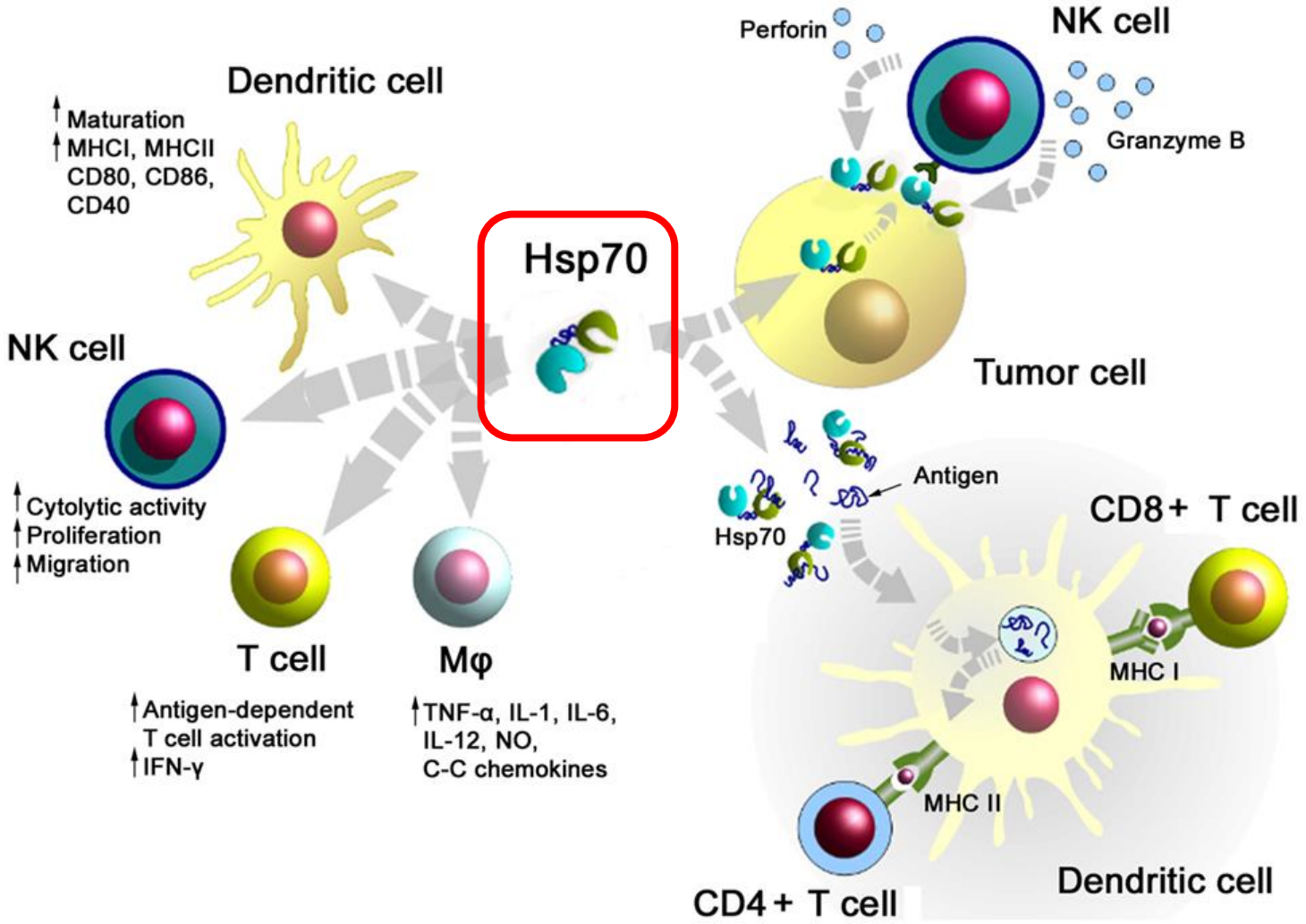
Huang CC et al, Unpublished data

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

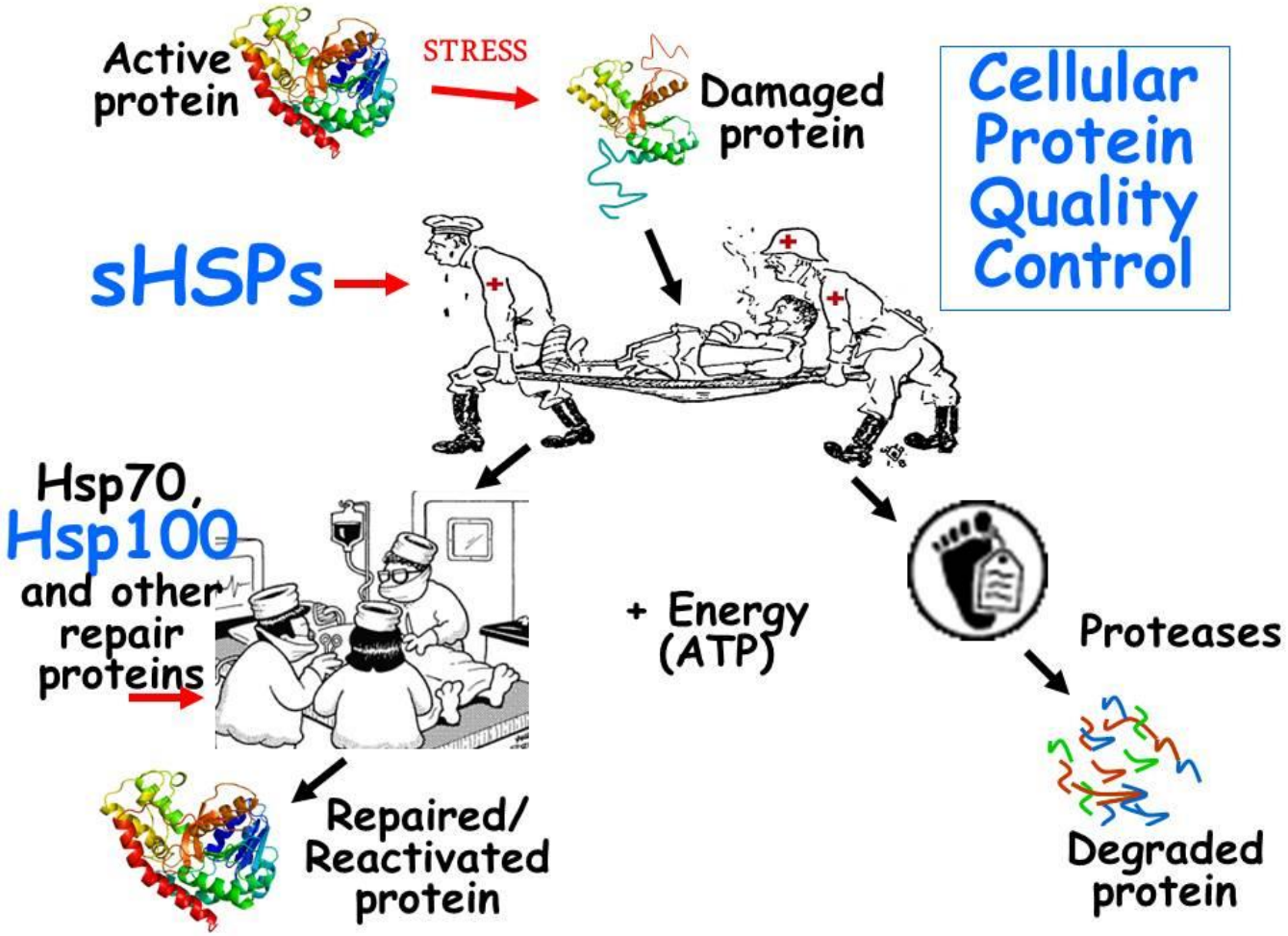
- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

Major immune modulatory functions of heat shock protein 70 (Hsp70)



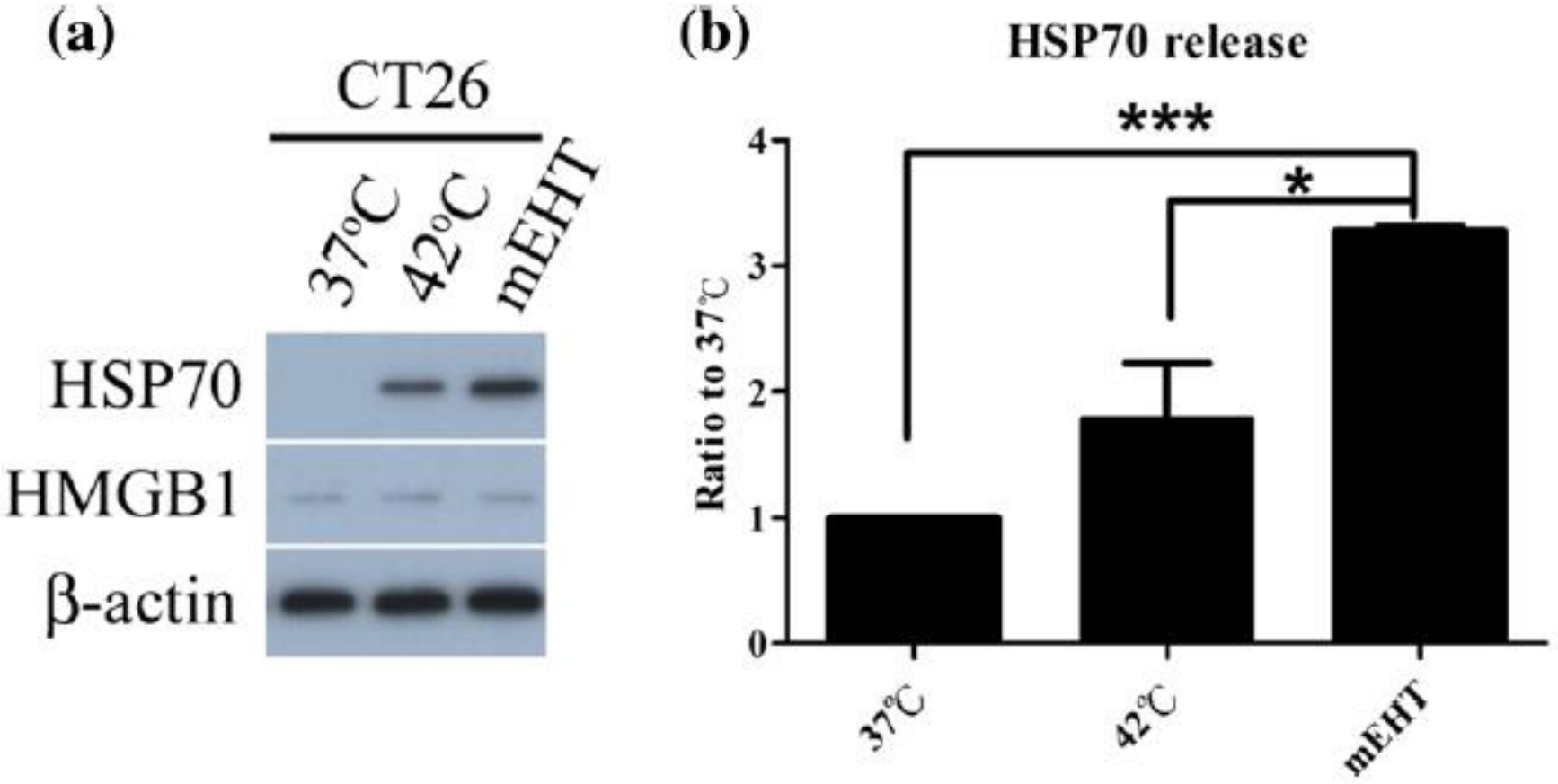
Shevtsov M and Multhoff G (2016) *Front. Immunol.* 7:171.

The protection role of HSP70 in cells under stress condition



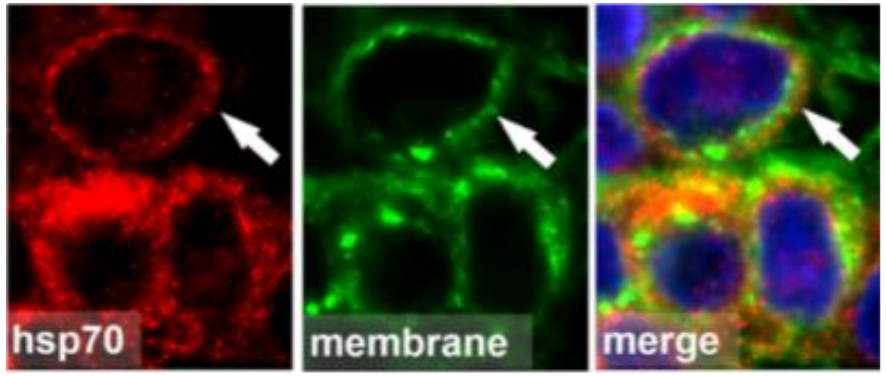
Dr. Elizabeth Vierling, University of Massachusetts

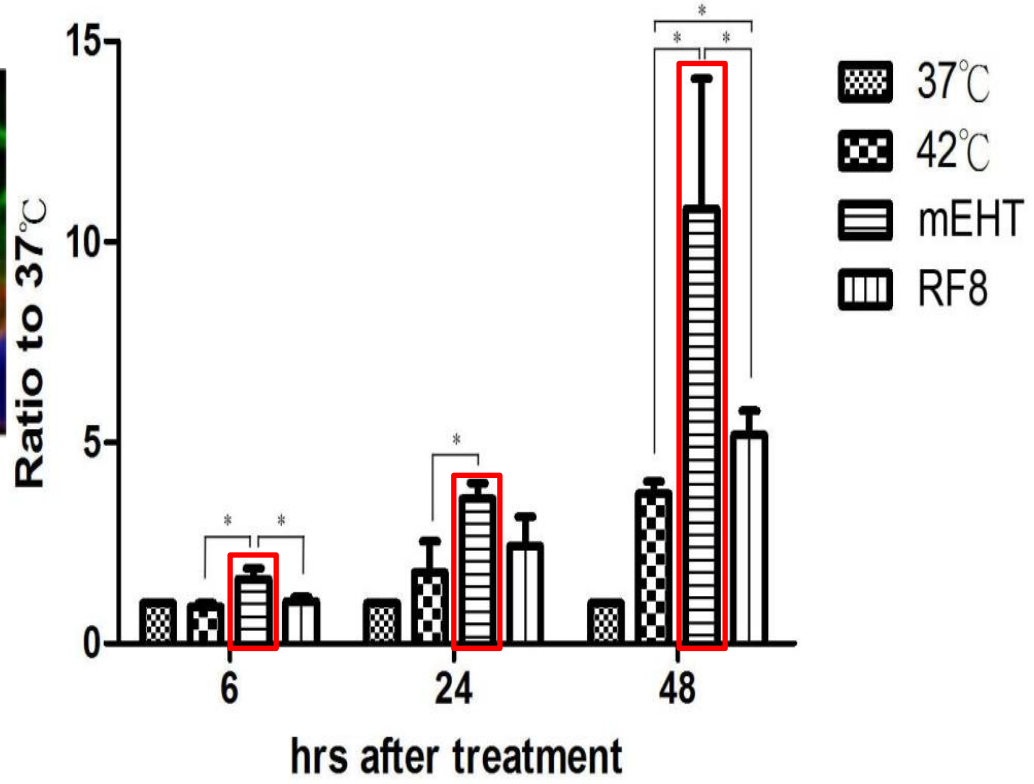
Stress protein analysis
The expression of HSP70



Tsang et al. BMC Cancer (2015) 15: 708

Stress protein analysis
The expression of HSP70





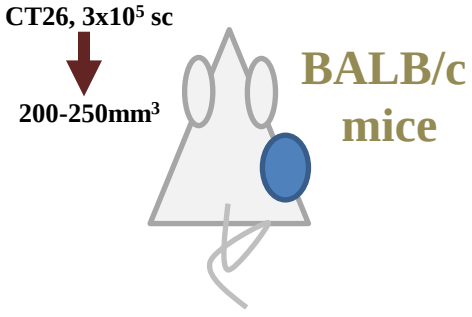
Yang KL et al, Oncotarget. 2016;7(51):84082-84092.

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

mEHT-DC Therapy Increases Tumor Infiltrating Leukocytes

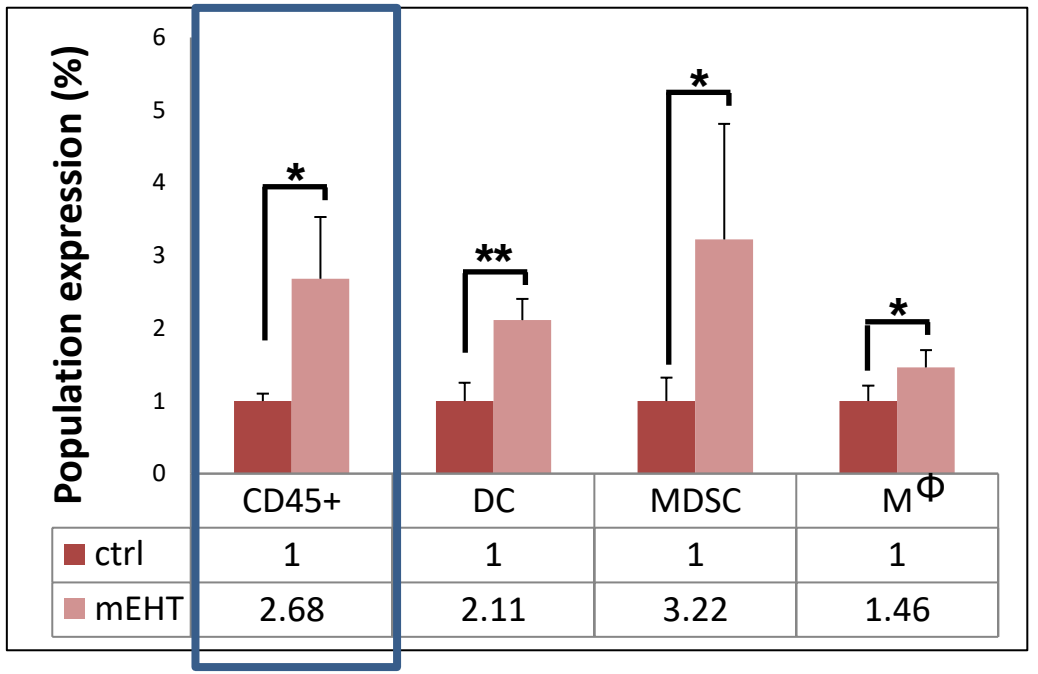


Group: 37,42mEHT

HT, 42°C 30min

Rest for 48h

Tumor were collected for TILs analysis



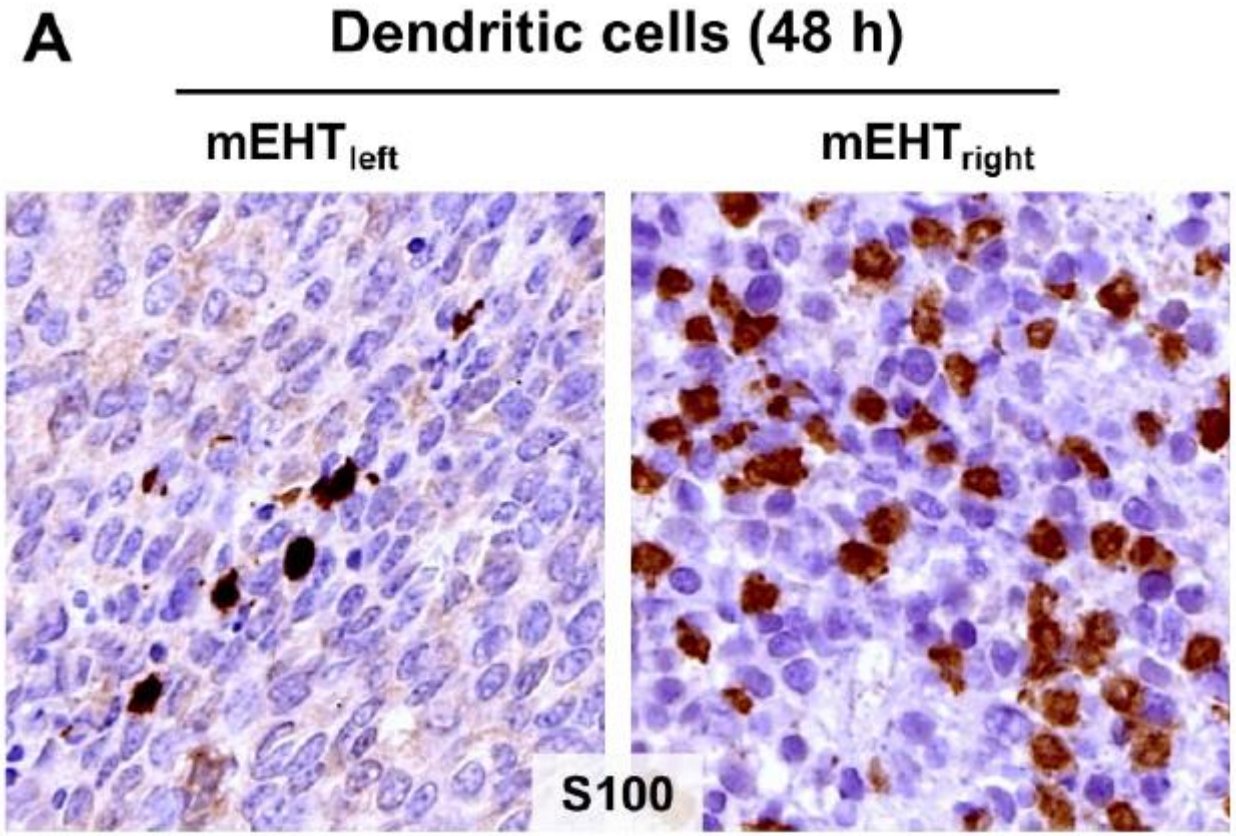
	CD45+	DC	MDSC	MΦ
ctrl	1	1	1	1
mEHT	2.68	2.11	3.22	1.46

48h after treatment

*** p<0.05, **p<0.01, ***p<0.001**

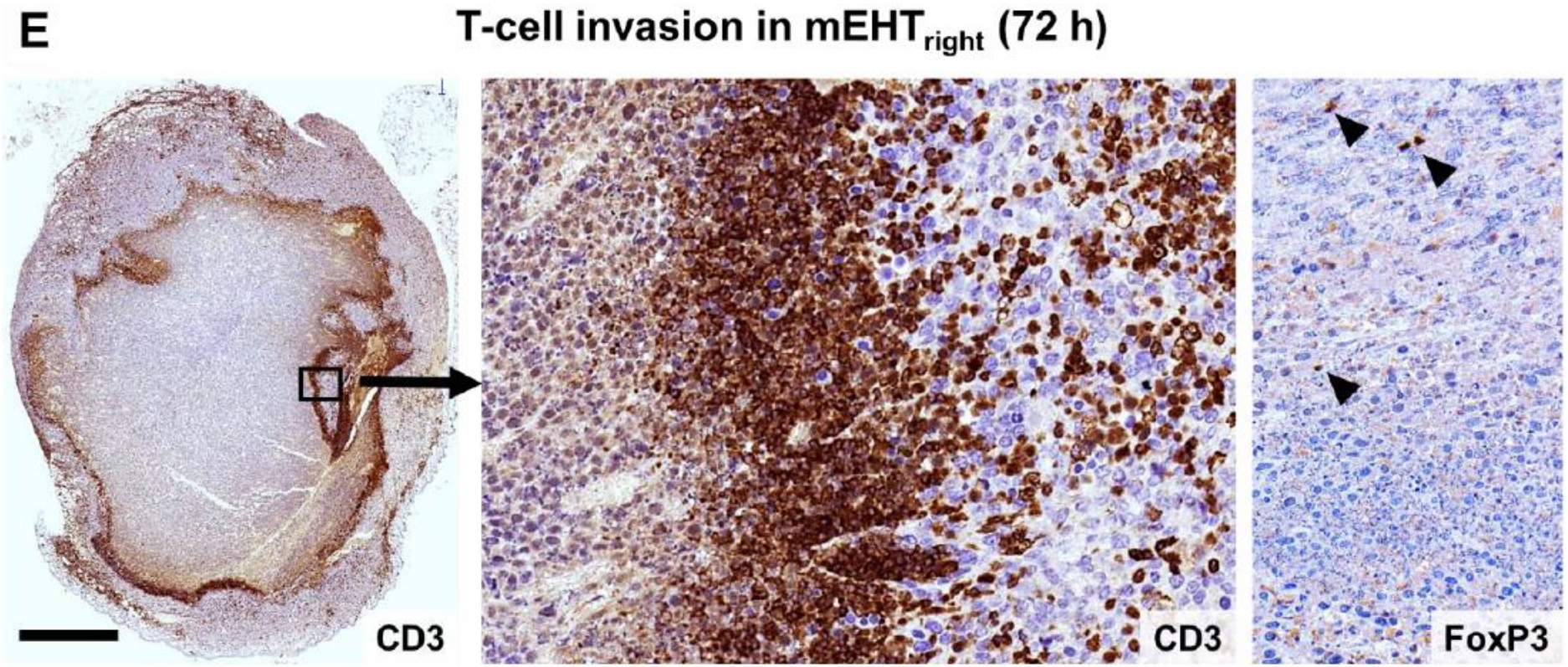
Huang CC et al, Unpublished data

Modulated-Electro-Hyperthermia Enhances DC infiltration

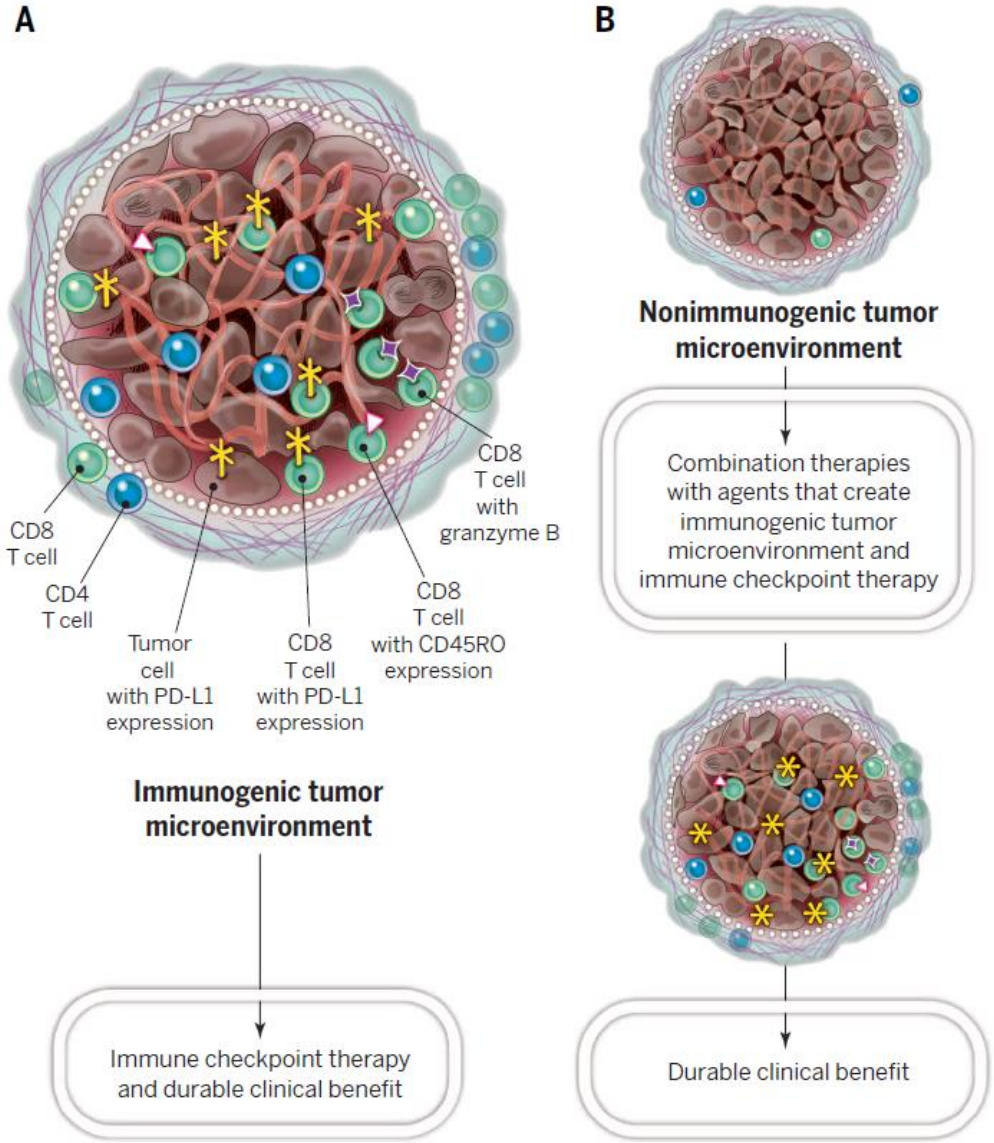


Tamas et al, Journal of Cancer. 2018;9:41-53.

Modulated-Electro-Hyperthermia Enhances T-cell infiltration



Tamas et al, Journal of Cancer. 2018;9:41-53.



Nonimmunogenic Tumors

mEHT + immune tx.

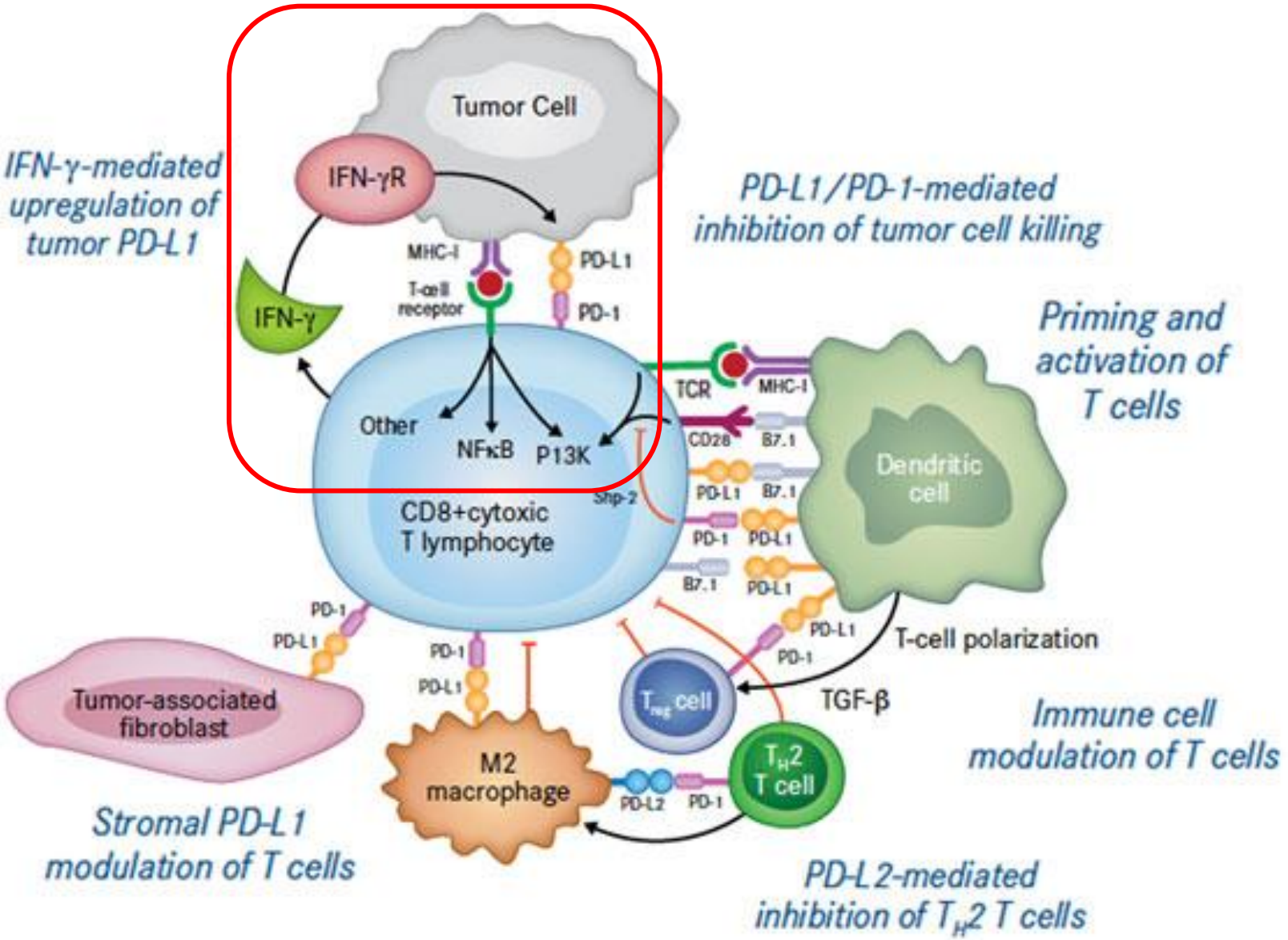
Immunogenic Tumors

Science 2015;348:56-61

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

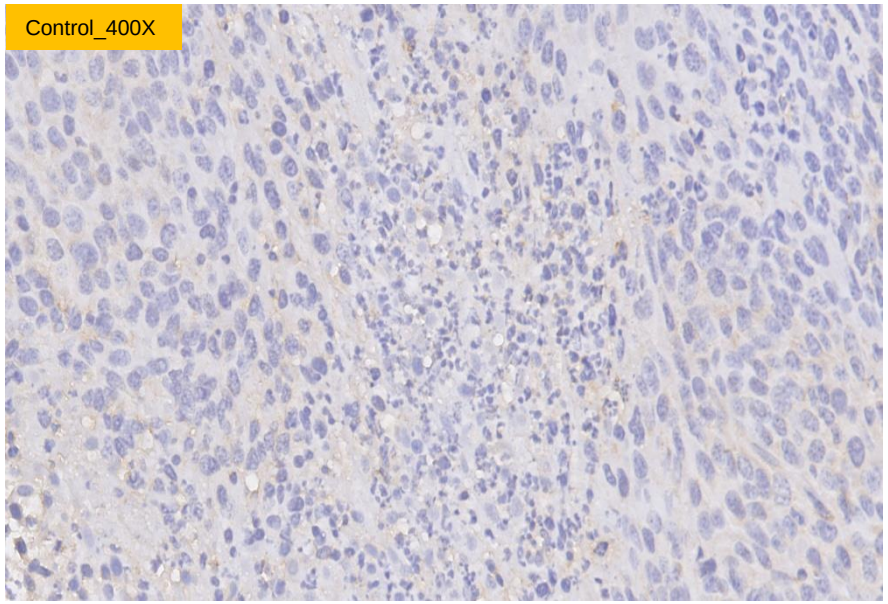
- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

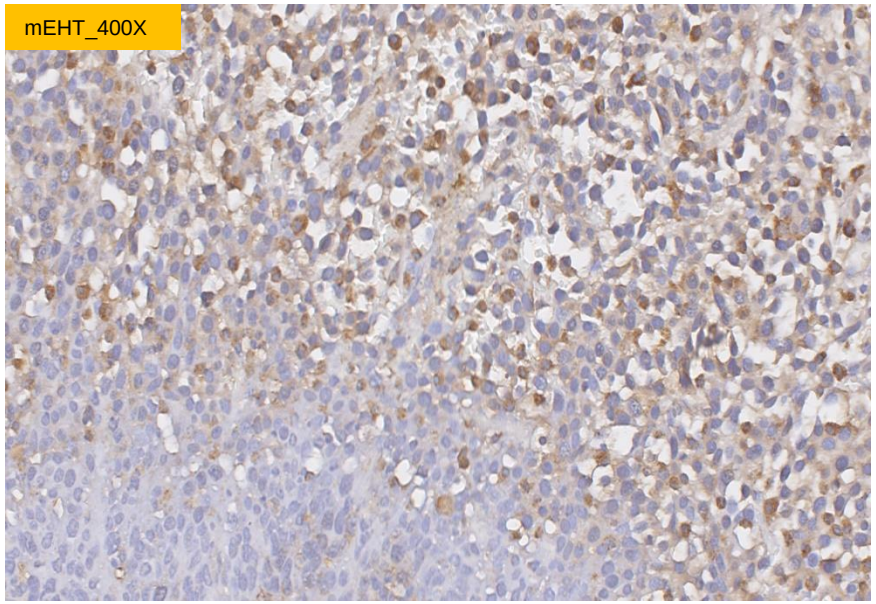
- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

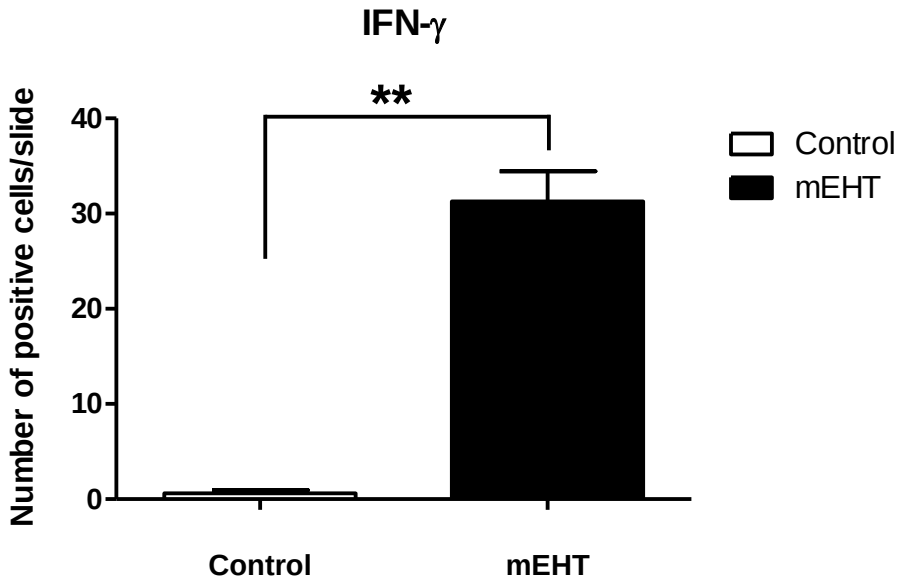


Clin Cancer Res. 2013;19:1021-1034.

Modulated-Electro-Hyperthermia Induced IFN-γ Production in Tumor







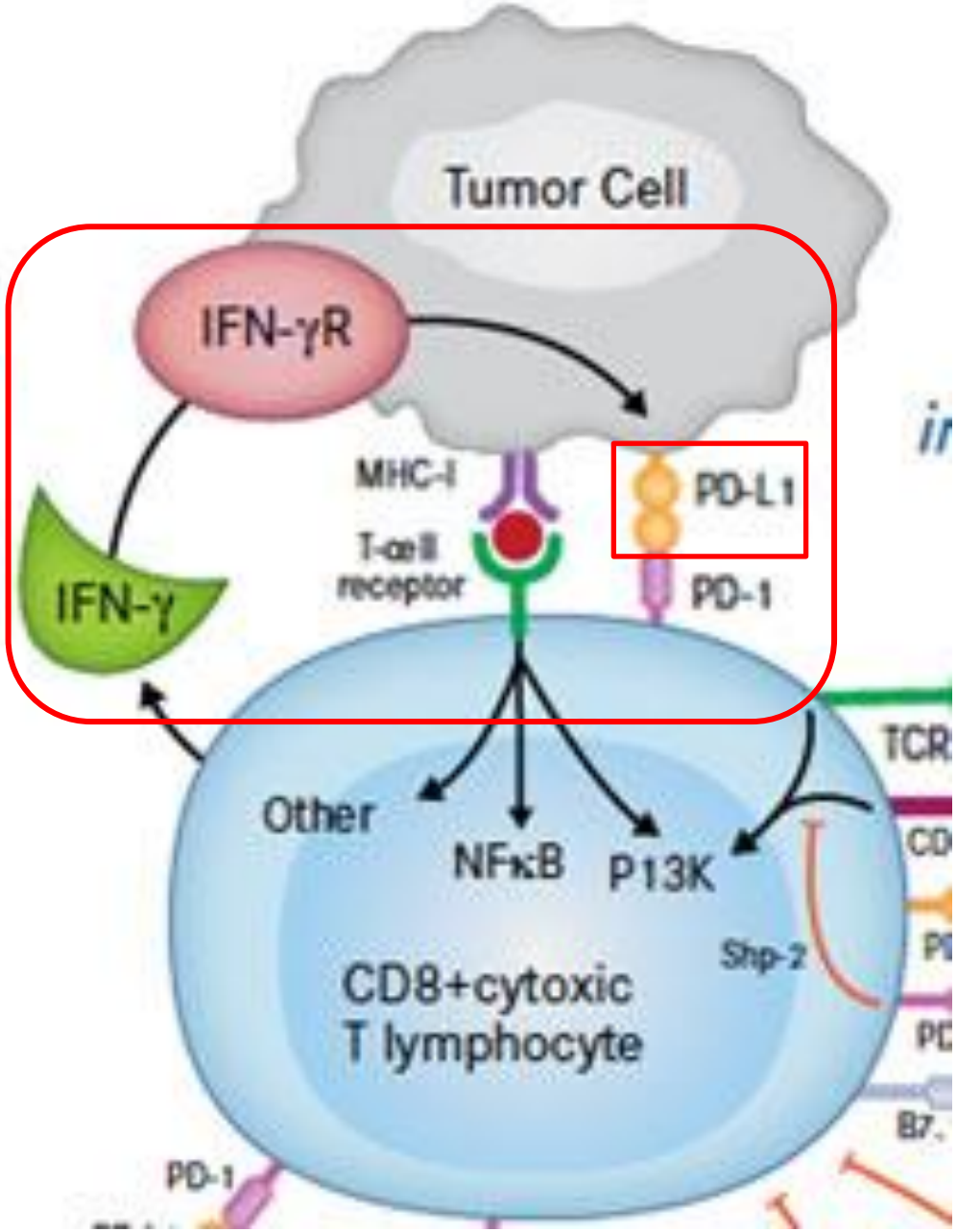
Wang YS et al, Unpublished data

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

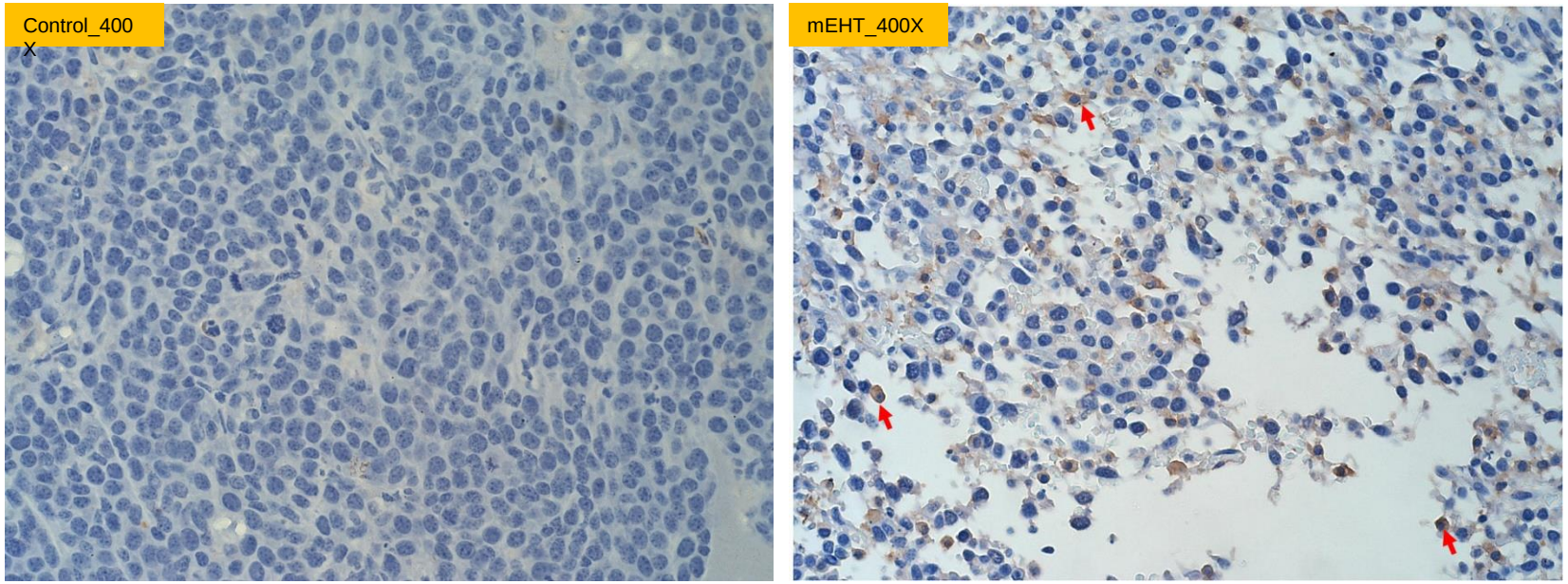
- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

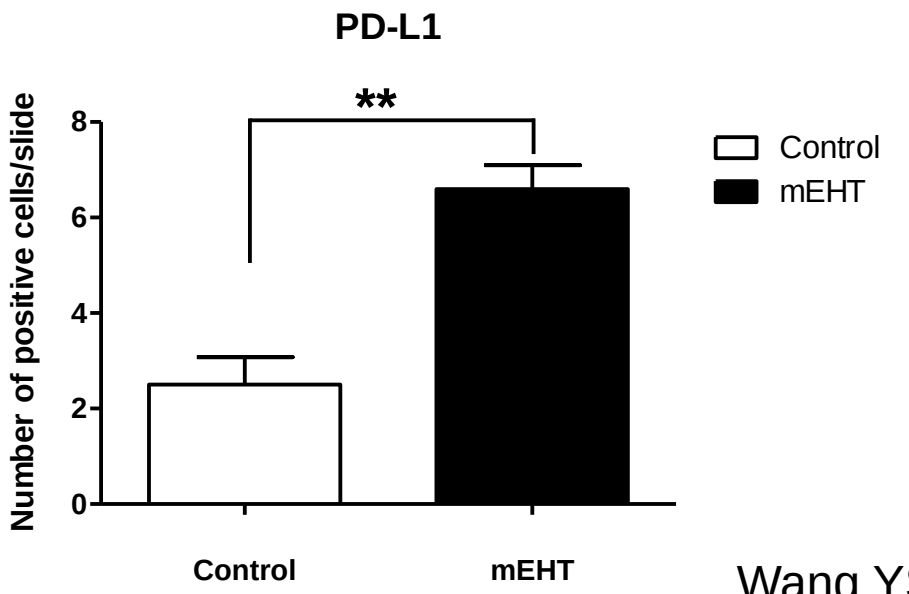
IFN-γ-mediated upregulation of tumor PD-L1



Clin Cancer Res. 2013;19:1021-1034.

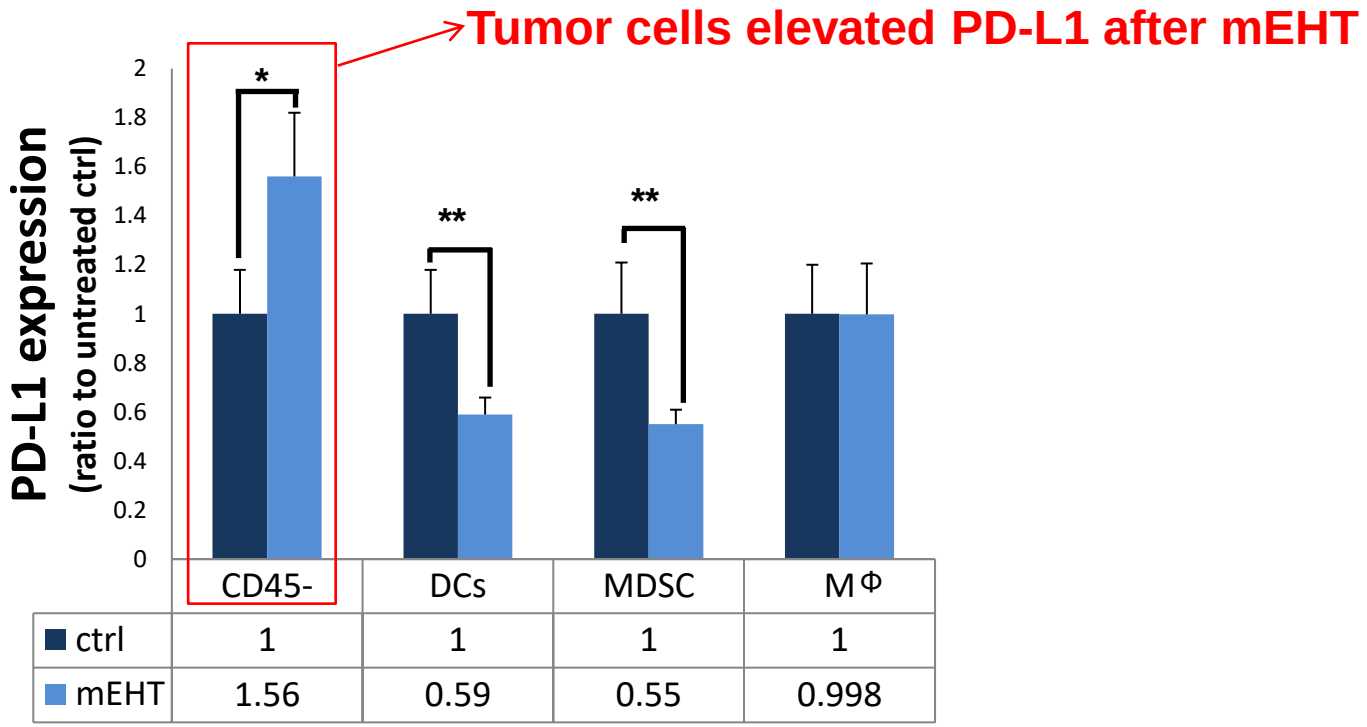
Oncothermia Induced PD-L1 Expression in Tumor





Wang YS et al, Unpublished data

The profile of PD-L1 expression in tumor microenvironment after Modulated-Electro-Hyperthermia treatment



48h after treatment

*** p<0.05, **p<0.01**

Group:

1. **untreated ctrl (n=4)**
2. **mEHT (n=6)**

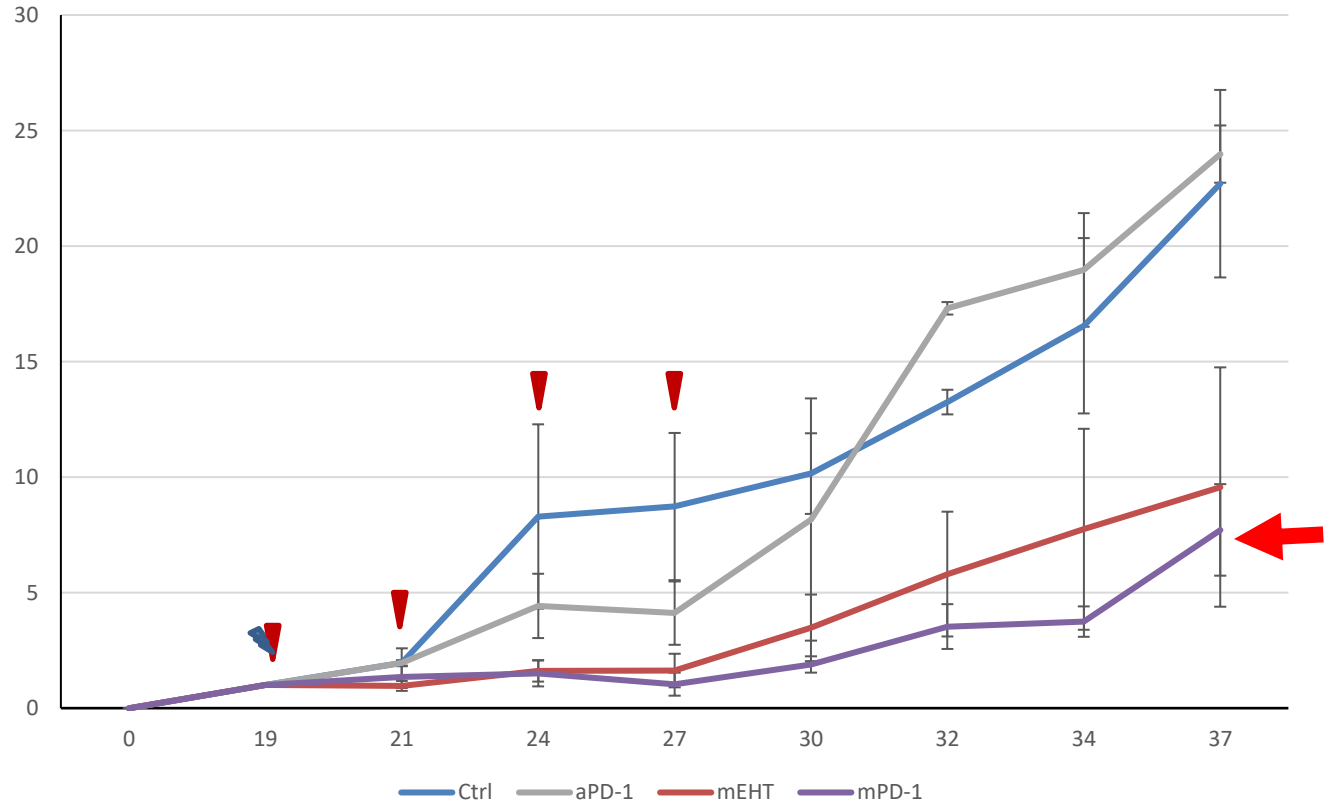
Wang YS et al, Unpublished data

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

Synergistic Effect with Anti-PD-1 Therapy



mEHT treatment: 42°C maintain 40 min.
αPD-1 Ab: IP 200ug per mice for 4 times.

Wang YS et al, Unpublished data

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

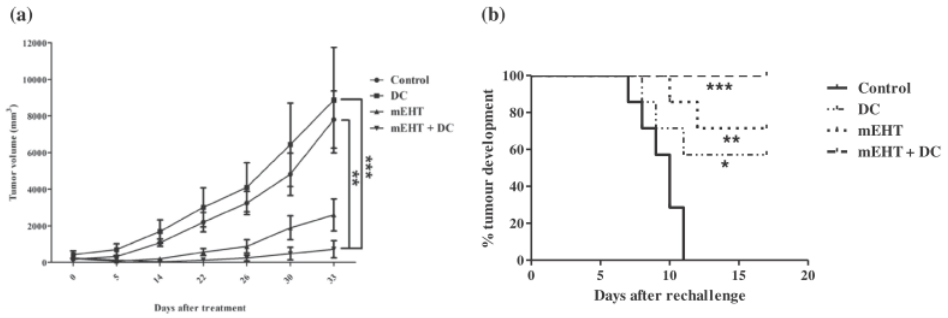
Tsang *et al. BMC Cancer* (2015) 15:708
DOI 10.1186/s12885-015-1690-2

BMC Cancer

RESEARCH ARTICLE Open Access

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

Yuk-Wah Tsang[1,2], Cheng-Chung Huang[3], Kai-Lin Yang[3], Mau-Shin Chi[3], Hsin-Chien Chiang[3], Yu-Shan Wang[3], Gabor Andocs[4], Andras Szasz[5], Wen-Tyng Li[2*] and Kwan-Hwa Chi[3,6*]



ONCOLOGY REPORTS 32: 2373-2379, 2014

Modulated electro-hyperthermia enhances dendritic cell therapy through an abscopal effect in mice

WEI QIN[1], YASUNORI AKUTSU[1], GABOR ANDOCS[2], AKIKO SUGANAMI[3], XIN HU[1], GULBOSTAN YUSUP[1], AKI KOMATSU-AKIMOTO[1], ISAMU HOSHINO[1], NAOYUKI HANARI[1], MIKITO MORI[1], YUKA ISOZAKI[1], NAOKI AKANUMA[1], YUTAKA TAMURA[1] and HISAHIRO MATSUBARA[1]

[1]Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba 260-8670; [2]Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori 680-8553; [3]Department of Bioinformatics, Graduate School of Medicine, Chiba University, Chiba 260-8670, Japan

Received July 2, 2014; Accepted August 25, 2014

DOI: 10.3892/or.2014.3500

Abstract. The aim of this study was to assess whether modulated electro-hyperthermia (mEHT) can induce an abscopal effect and thereby enhance the antitumor effects of immunotherapy. We used an intratumoral dendritic cell (DC) injection and mEHT to treat C3H/He mice inoculated with squamous cell carcinoma SCCVII cells in the left leg, and we assessed the whole body antitumor effects. Tumors were examined every two or three days in order to assess growth inhibition. The tumor-draining lymph nodes were removed to enable flow cytometric analysis of $CD3^+$ and $CD8^+$ cells, whereas immunohistochemistry was used to assess CD8, S100 and Foxp3 expression in the tumors. Additionally, GP96 expression in the tumors from the different treatment groups was measured. In the control group, the mean tumor volume was larger than that in other groups. These results indicated that the combination therapy of an intratumoral DC injection and mEHT evoked systemic antitumor activity. A larger number of $CD3^+$ and $CD8^+$ cells were detected by flow cytometric analysis in the DC plus mEHT treatment group. Tumor tissue immunostaining showed that CD8 and S100 were more strongly expressed in the DC plus mEHT treatment group, although Foxp3 expression was much higher in the control group. The GP96 gene expression level in the mEHT group was significantly different from the expression level in the control group. An abscopal effect may be induced by mEHT, and the effect of immunotherapy with DCs was strongly enhanced by the overexpression of GP96. GP96 is thought to be one of the molecules explaining the abscopal effect. Direct intratumoral administration of DCs and mEHT may be a feasible future treatment strategy.

Correspondence to: Dr Yasunori Akutsu, Department of Frontier Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, 240-8470, Japan
E-mail: yakutsu@faculty.chiba-u.jp

Key words: dendritic cells, hyperthermia, abscopal effect, cancer therapy, immunotherapy

Introduction

The abscopal effect is a phenomenon noted in the treatment of metastatic cancer where localized irradiation of a tumor causes shrinking not only of the immediate target, but also of tumors located far from the irradiated area. This phenomenon is extremely rare, but when it does occur, its anticancer effects can be dramatic, leading to the disappearance of malignant growths throughout the body. Such success has been described for a variety of malignancies, including melanoma, lymphoma, and lung metastases of hepatocellular carcinoma (1-3). The mechanism underlying the abscopal effect remains to be clarified, although a variety of underlying biological events may be responsible, particularly those induced by the immune system (4). In mouse studies, the observations support the immune hypothesis for the abscopal effect (5-7).

The modulated electro-hyperthermia (mEHT) system is a fast-developing complementary treatment method that is effective against different types of tumors (8,9). The principles involved are based on the classical method of hyperthermia, but the aim, besides the absolute increase in temperature, is to promote the direct absorption of electric-field energy by the extracellular fluid, thereby destroying the membrane of cancer cells.

Hyperthermia is usually applied as an adjunct to an already established treatment modality, such as radiotherapy and chemotherapy, in order to achieve tumor temperatures of 40-46˚C. Hyperthermia was originally controlled through modulating temperature alone, whereas the more recently developed mEHT (also described as 'oncothermia') is based on energy dose control, replacing the single temperature concept (9).

Although hyperthermia has been extensively studied, the effects of mEHT combined with dendritic cell (DC) treatment on squamous cell carcinoma have not been addressed. The goal of this study was to evaluate the antitumor effects of combined direct intratumoral injection of DCs and mEHT treatment using a mouse squamous cell carcinoma (SCCVII) cancer model. We showed that this combined treatment causes both local and distant shrinkage of SCCVII-derived tumors,

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia

Kai-Lin Yang[1,2,3], Cheng-Chung Huang[1], Mau-Shin Chi[1], Hsin-Chien Chiang[1], Yu-Shan Wang[1], Chien-Chung Hsia[4], Gabor Andocs[5], Hsin-Ell Wang[6], Kwan-Hwa Chi[1,2,3,6]

[1]Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
[2]Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei, Taiwan
[3]School of Medicine, Fu Jen Catholic University, New Taipei, Taiwan
[4]Institute of Nuclear Energy Research, Taoyuan, Taiwan
[5]Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Japan
[6]Institute of Veterinary Clinical Science, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan

Correspondence to: Kwan-Hwa Chi, **email:** M006565@ms.skh.org.tw
Hsin-Ell Wang, **email:** hewang@ym.edu.tw

Keywords: *modulated electro-hyperthermia, conventional capacitive coupling hyperthermia, water bath, cytotoxicity, cell membrane*

Received: *May 03, 2016* ***Accepted:*** *August 11, 2016* ***Published:*** *August 20, 2016*

ABSTRACT

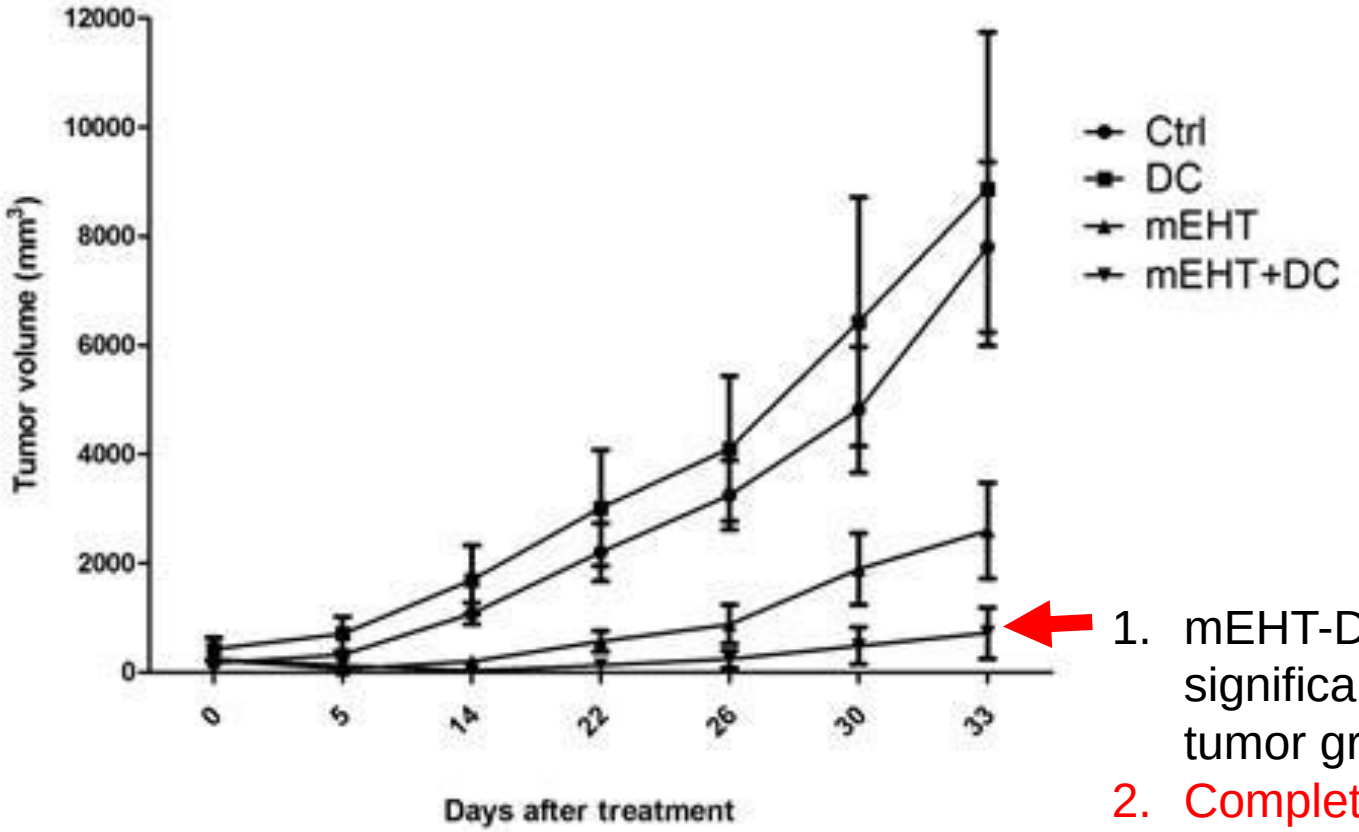
Radiofrequency-induced hyperthermia (HT) treatments for cancer include conventional capacitive coupling hyperthermia (cCHT) and modulated electro-hyperthermia (mEHT). In this study, we directly compared these methods with regard to *in vitro* cytotoxicity and mechanisms of action under isothermal conditions. Hepatoma (HepG2) cells were exposed to HT treatment (42°C for 30 min) using mEHT, cCHT or a water bath. mEHT produced a much higher apoptosis rate (43.1% ± 5.8%) than cCHT (10.0% ± 0.6%), the water bath (8.4% ± 1.7%) or a 37°C control (6.6% ± 1.1%). The apoptosis-inducing effect of mEHT at 42°C was similar to that achieved with a water bath at 46°C. mEHT also increased expression of caspase-3, 8 and 9. All three hyperthermia methods increased intracellular heat shock protein 70 (Hsp70) levels, but only mEHT greatly increased the release of Hsp70 from cells. Calreticulin and E-cadherin levels in the cell membrane also increased after mEHT treatment, but not after cCHT or water bath. These results suggest that mEHT selectively deposits energy on the cell membrane and may be a useful treatment modality that targets cancer cell membranes.

INTRODUCTION

Hyperthermia (HT), which involves the use of different techniques to achieve a fever-like temperature (≤ 42°C) around tumors [3, 4], has been used mainly in combination with radiotherapy or chemotherapy as a cancer treatment [1, 2]. Radiofrequency (RF) treatments, in which a pair of capacitive electrodes are placed on opposite sides of the body, are the most common methods for heating deep-seated tumors. Conventional capacitive coupling hyperthermia (cCHT), delivered using devices like the Thermotron RF-8, has been widely used in oncological practice for more than 2 decades in Japan. This device produces dielectric heat with high power via rapid changes in the electric field (8 MHz) to reach a goal temperature in a specific region [5]. However, maintaining a temperature of ≤ 42˚C for 30 to 60 minutes is generally not enough to cause the desired cytotoxicity. A previous study reported that, while cCHT alone resulted in complete responses in 14 out of 187 cases (7.5%), cCHT in conjunction with either radiotherapy, chemo-radiotherapy, or chemotherapy resulted in complete responses in 134 out of 270 (49.6%), 92 out of 244 (37.7%), and 54 out of 360 (15.0%) cases, respectively [6].

Modulated electro-hyperthermia (mEHT, trade name Oncothermia) is a new loco-regional electromagnetic hyperthermia method that uses a capacitive-impedance coupled 13.56 MHz RF current to selectively target

Combination of mEHT induced local anti-tumor effect of DC therapy in vivo

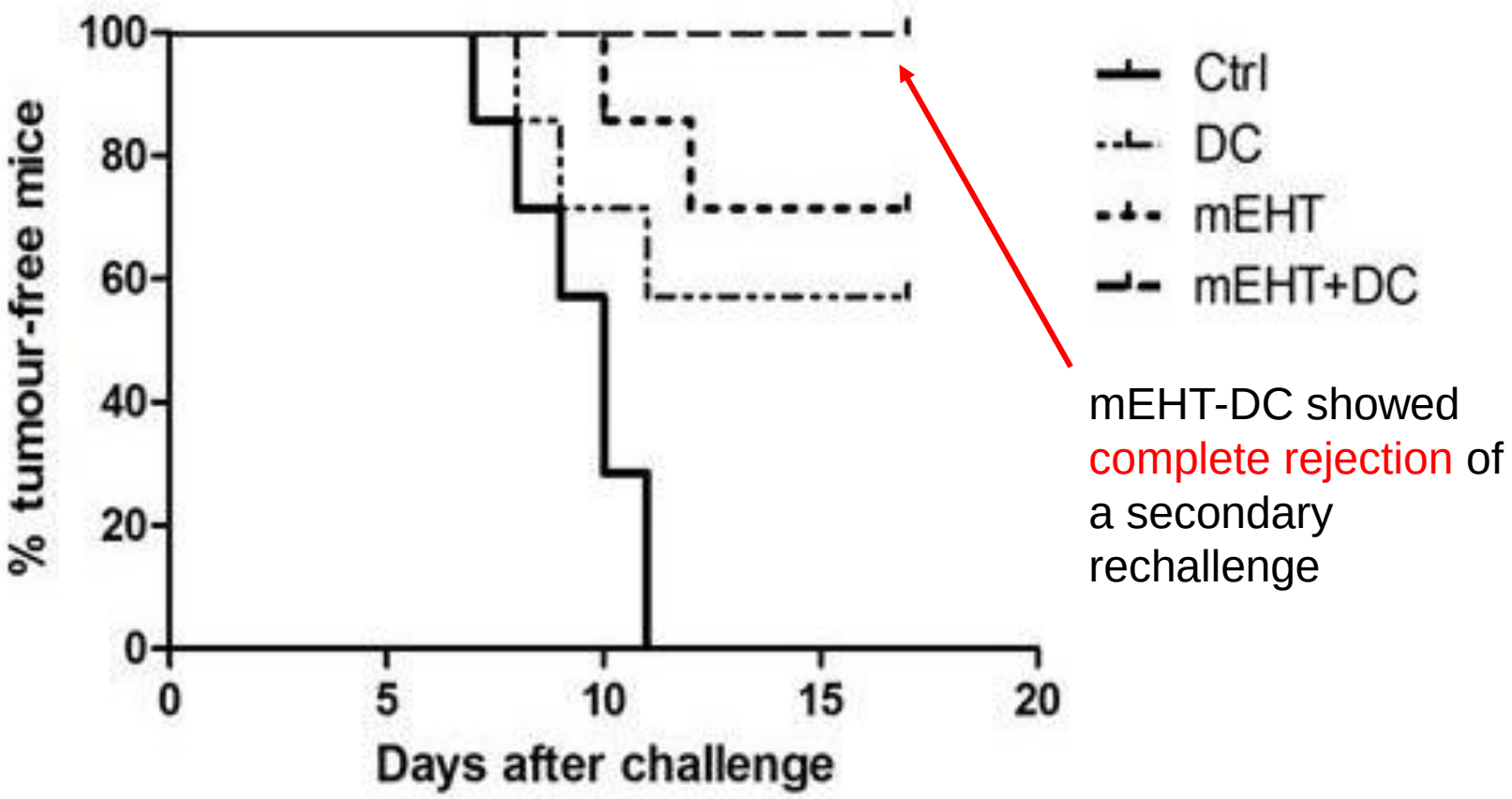


1. mEHT-DC therapy significantly delayed local tumor growth.
2. Complete tumor regression was observed in 5 out of 7 mice in this group.

Tsang et al. BMC Cancer 2015; 15:708

Combination of mEHT induced systemic anti-tumor effect of DC therapy in vivo

Rechallenge a secondary tumor one month later



mEHT-DC showed complete rejection of a secondary rechallenge

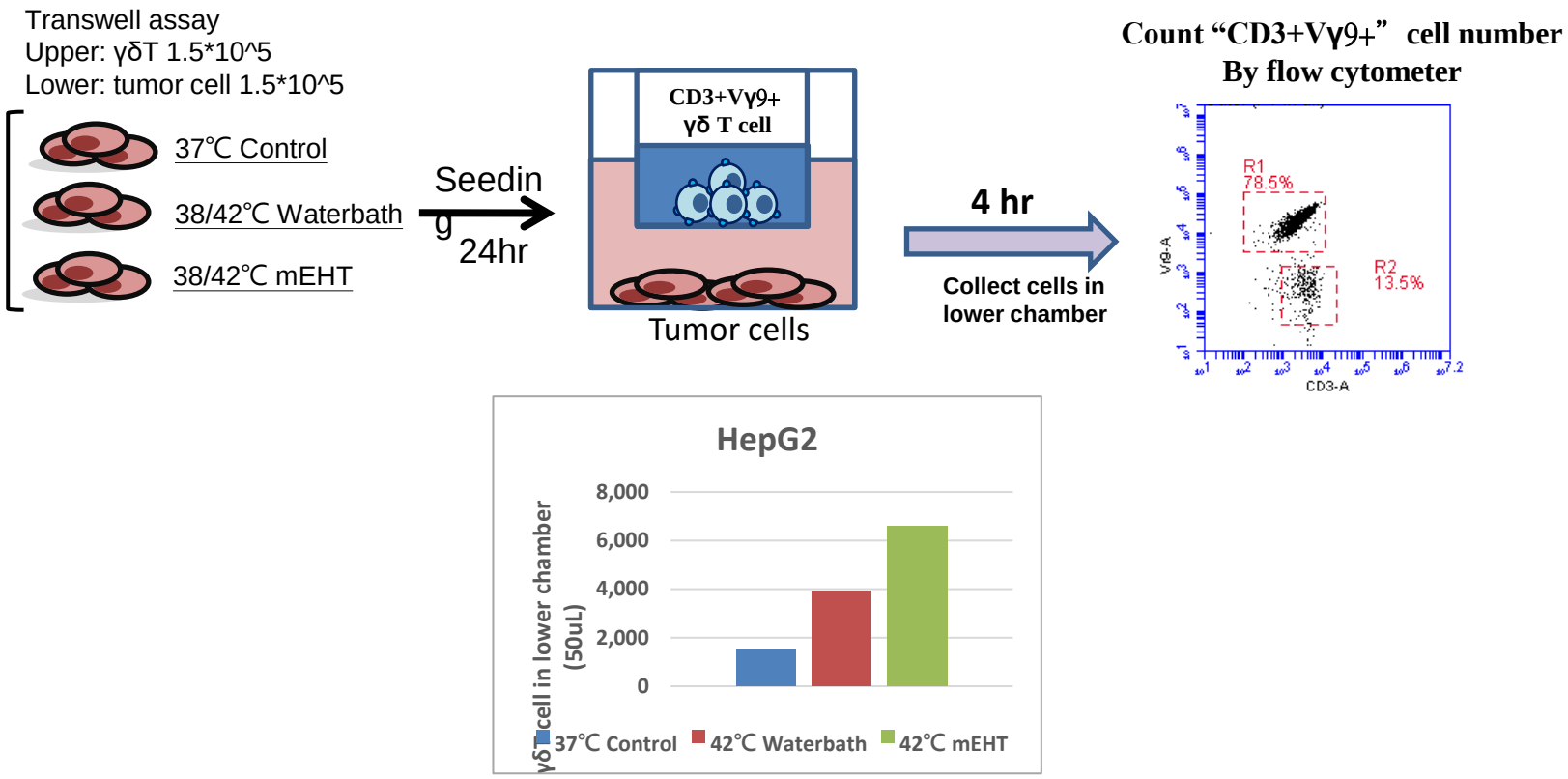
Tsang et al. BMC Cancer 2015; 15:708

Unique Immune Characteristics of Modulated-Electro-Hyperthermia

- Induce Apoptosis
- Release HSP70
- Increase Tumor Infiltrating Leukocytes
- Production of IFN-γ
- Increase PD-1/PD-L1 Expression
- Synergistic Effect with Immune checkpoint Therapy

- Modulated-Electro-Hyperthermia plus Cell therapy
  - Synergistic Effect with Dendritic Cells
  - Synergistic Effect with Gamma Delta T Cells

To assess the migration ability of γδT cells indirect contact with mEHT treated tumor cells

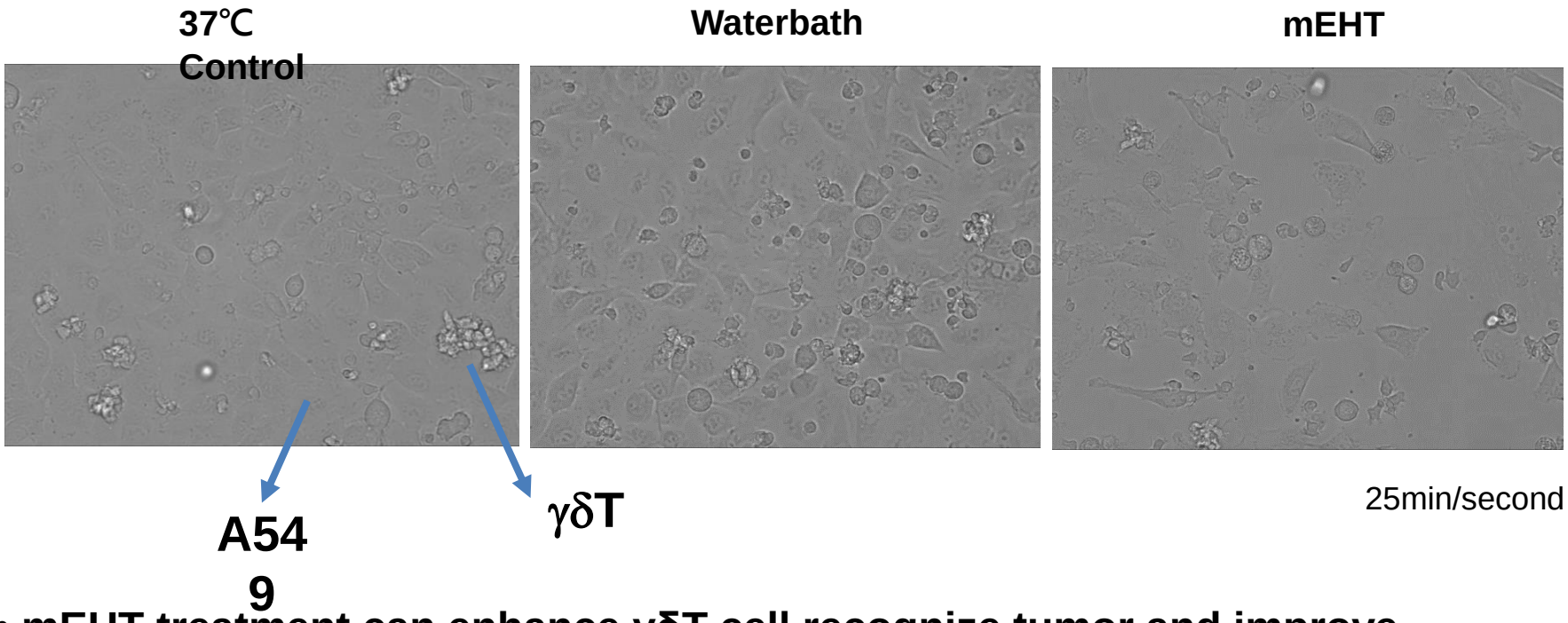


- **mEHT treatment can enhance γδT cell migration towards tumor cells**

Huang CC et al, Unpublished data

The cytotoxicity of γδT cells on mEHT treated tumor cells

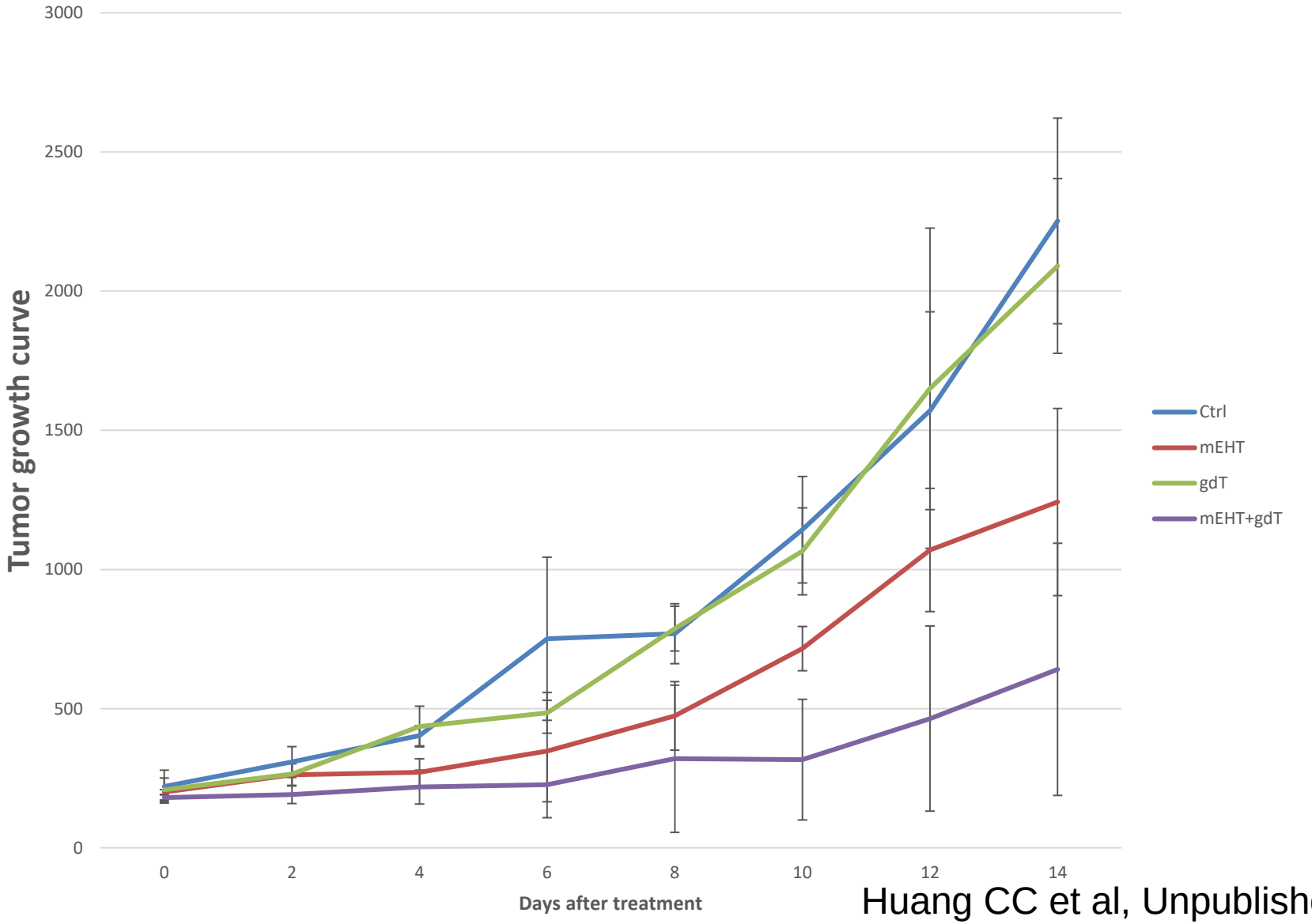
A549 with γδT during 16hr coculture



- **mEHT treatment can enhance γδT cell recognize tumor and improve antitumor activity**

Huang CC et al, Unpublished data

Combination of mEHT induced local anti-tumor effect of γδT cell therapy in vivo



Huang CC et al, Unpublished data

電熱治療之適應症

科別	適應症
血腫科	有遠端轉移需化療的癌症病人
大腸直腸科	大腸直腸癌
外科	乳房癌
泌尿科	膀胱癌，前列腺癌
婦科	子宮頸癌，卵巢癌，子宮內膜癌
肝膽腸胃科	胰臟癌，肝癌，胃癌
胸外 神外	肺癌，食道癌 腦癌
禁忌及不適用	體內或治療區域附近有金屬部件，心臟節律器、懷孕、無法溝通配合、對溫度感覺異常、epilepsy的病人

電 熱 治 療 頻 率 及 所 需 時 間

- 每次 60分鐘（一小時）
- 每星期一至三次，每次隔４0小時以上，每星期 ＞3次無益！
- 一療程 6 至 10次（平均 8 次），總次數無上限，無所謂「累積熱毒性」！

熱療、放療、化療的次序

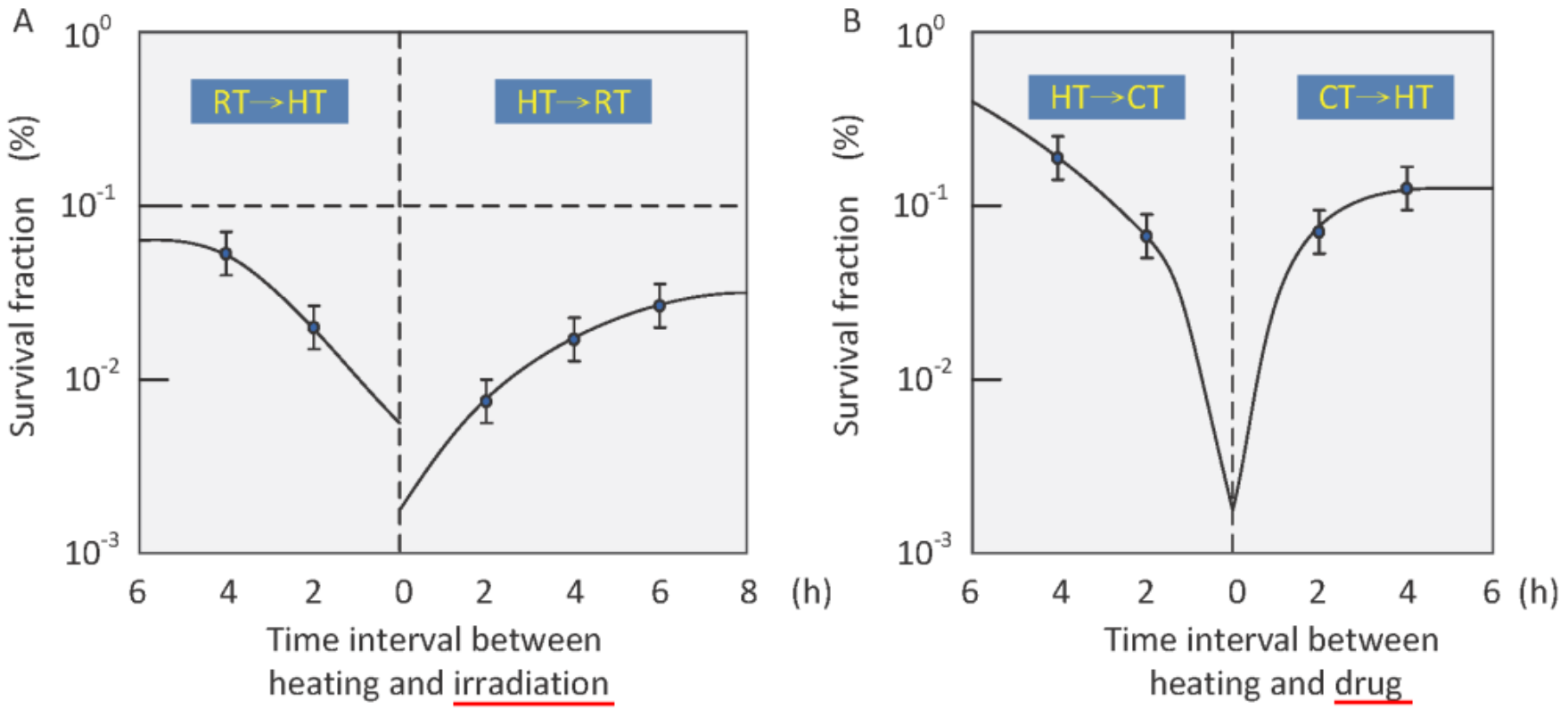


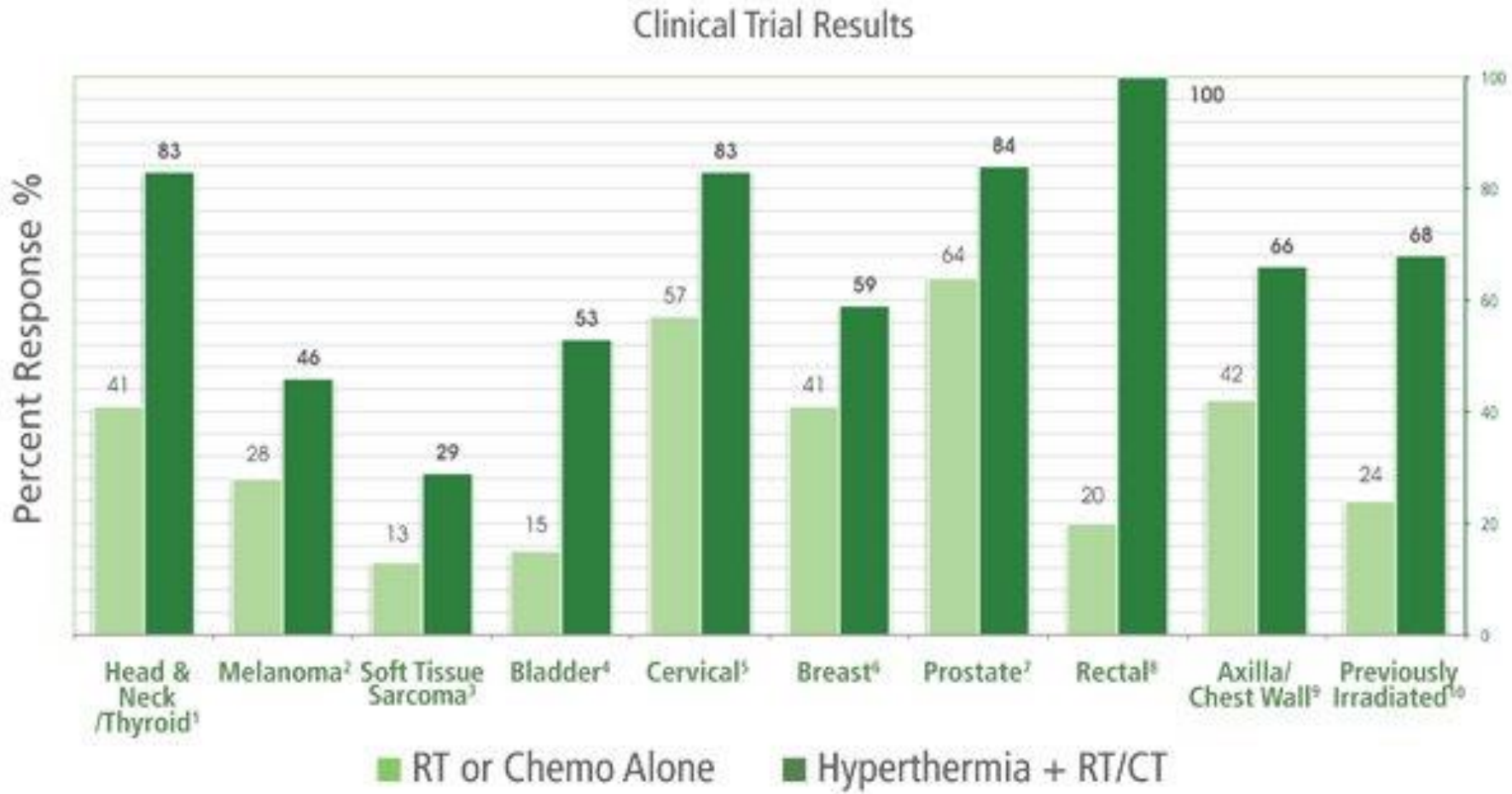
FIGURE 3. Qualitative schematic diagrams of effect of treatment intervals and sequences for combined radiation/drug and hyperthermia. A, Radiation and heat sequence; B, chemotherapy and heat sequence, effect of supra-additive drugs. Survival fraction is the colonies counted divided by the number of colonies plated with a correction for the plating efficiency. RT, radiation therapy; HT, heat therapy; CT, chemotherapy.

Critical Reviews™ in Biomedical Engineering, 38(1):101–116 (2010)



熱療有實証嗎?

Hyperthermia Improves Response Rates When Used As A Combined Therapy



[1] Valdagni et al.,1994 | [2] Overgaard et al.,1995 | [3] Issels et al., 2010 | [4] Colombo et al.,2011 | [5] Van der Zee., 2000

[6] Vernon et al.,1996 | [7] Hurwitz et al., 2011 | [8] Kakehi et al.,1990 | [9] Jones et al., 2005 | [10] Vernon et al.,1996

Oncothermia vs SEER Data Base

NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

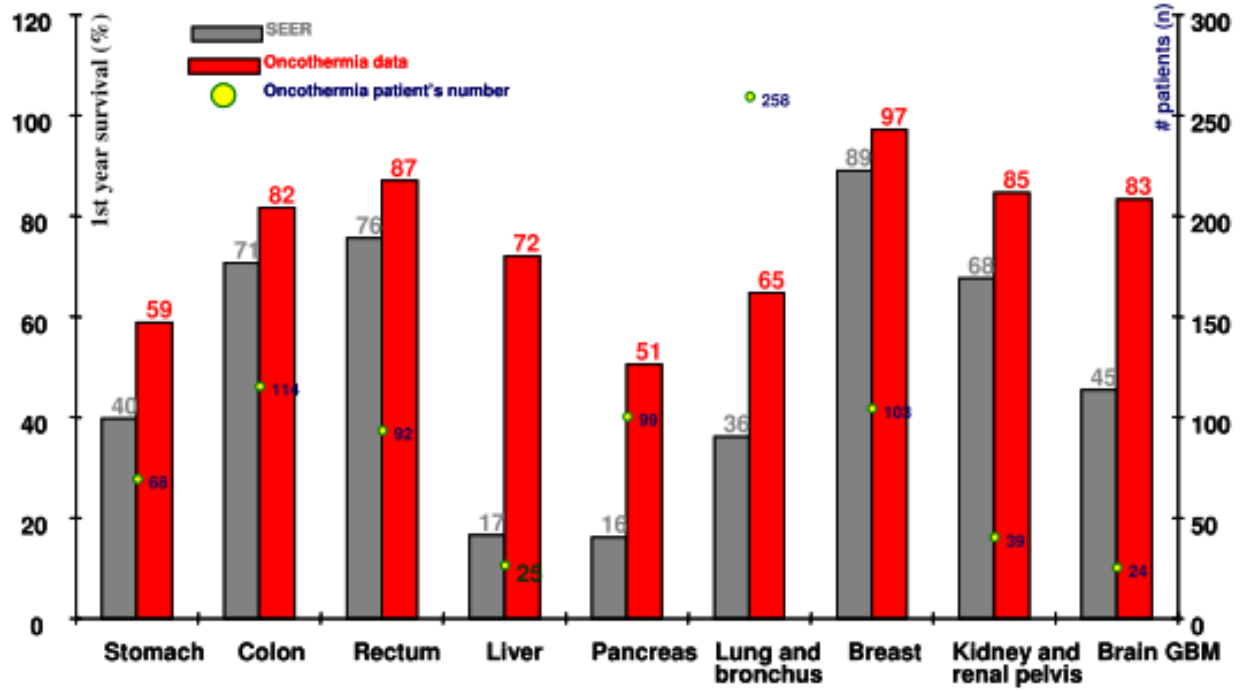


Fig. 14. Comparison of the first-year survival rates of various cancers with the large SEER database

Response Rate and Survival Based on **Oncotherm Data**

Table 1: Collection of the studies (phase II) made by oncothermia in combination with various conventional oncotherapies. (Data are weighted averages of the study results.)

有反應病人平均存活　　沒反應病人平均存活

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of nonresponding patients (m)
Brain studies	10	521	73.99	22.19	44.09	51.31	15.88
Pancreas studies	6	184	47.04	11.02	53.05	28.09	7.58
Lung studies	5	636	64.76	15.79	25.73		
Bone	3	79		40.10	90.90		
Liver metastasis	7	267	86.00	18.06	80.00		
Colorectal	7	447			63.18	109.80	23.20
Gynecology (pelvic)	5	100	93.22	33.25	44.82	89.36	21.70
Breast	1	103	97.10	52.10	45.00	274.80	10.90
Esophagus	2	19	41.70	55.64	35.00	29.40	8.50
Stomach study	1	68	58.90	14.40			
Kidney cancer	1	39	84.60	35.90	48.00	78.40	33.70
Urinary bladder cancer	1	18	85.00	36.50	73.00	42.00	22.60
Head and neck	1	64	92.20	26.10			
Soft tissue sarcoma	1	16	100.00	35.90	31.00	115.30	31.30
Prostate	3	135	88.90	38.80	72.00	53.40	7.60
SUM	54	2796			51.63		

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 159570, 20 pages
http://dx.doi.org/10.1155/2013/159570

Cervix Cancer: Cochrane Systemic Review

Cochrane Library

Cochrane Database of Systematic Reviews

2015

Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma (Review)

Lutgens L, van der Zee J, Pijls-Johannesma M, De Haas-Kock DFM, Buijsen J, van Mastrigt GAPG, Lammering G, De Ruysscher DKM, Lambin P

References to studies included in this review

Chen 1997 *{published data only}*
* Chen HW, Fan JJ, Luo W. A randomized trial of hyperthermo-radiochemotherapy for uterine cervix cancer. *Chinese Journal of Clinical Oncology* 1997;**24**(4):249–51.

Datta 1987 *{published data only}*
* NR Datta, AK Bose, HK Kapoor. Thermoradiotherapy in the management of Carcinoma Cervix (Stage IIIB): A controlled Clinical Study. *Indian Medical Gazette* 1987; **121**:68–71.

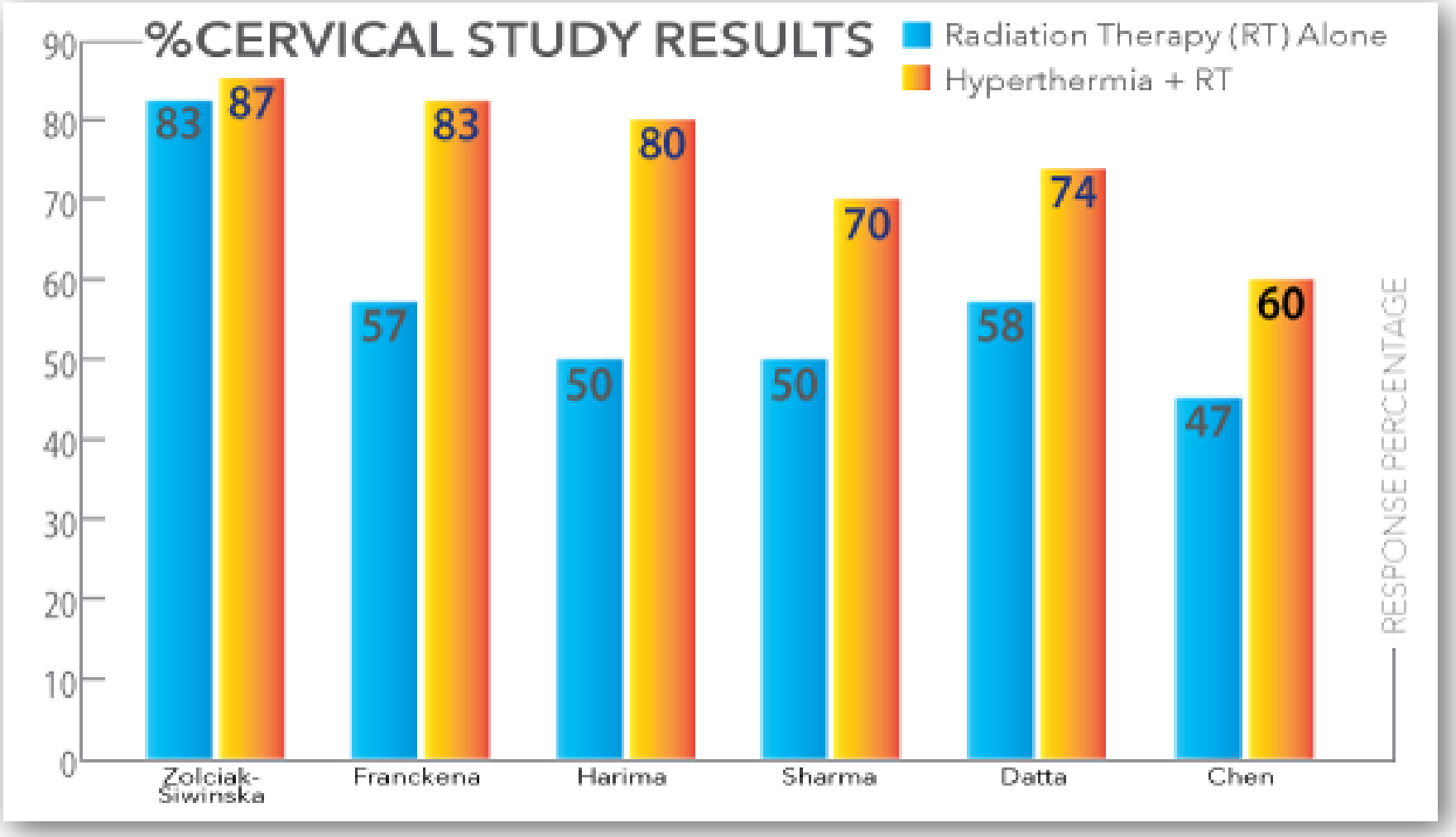
Harima 2001 *{published data only}*
* Harima Y, Nagata K, Harima K, Ostapenko VV, Tanaka Y, Sawada S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *International Journal of Hyperthermia the Official Journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group* 2001;**17**(2):97–105. [MEDLINE: Index-Medicus]

Sharma 1991 *{published data only}*
* Sharma S, Singhal S, Sandhu AP, Ghoshal S, Gupta BD, Yadav NS. Local thermo-radiotherapy in carcinoma cervix: improved local control versus increased incidence of distant metastasis. *Asia Oceania Journal of Obstetrics and Gynaecology AOFOG* 1991;**17**(1):5–12.

van der Zee 2000 *{published data only}*
* Van der Zee J, Gonzalez-Gonzales D, Van RGC, Van DJDP, Van PWLJ, Hart AAM. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. *Lancet* 2000;**355**(9210):1119–25.

Vasanthan 2005 *{published data only}*
* Vasanthan A, Mitsumori M, Park JH, Zhi Fan Z, Yu Bin Z, Oliynychenko P, et al. Regional hyperthermia combined with radiotherapy for uterine cervical cancers: A multi-institutional prospective randomized trial of the international atomic energy agency. *International Journal of Radiation Oncology, Biology, Physics* 2005;**61**(1):145–53.

Cervix Cancer



Source: Cochrane Systemic Review

Cervix Cancer

Clinical Evidence

Tumor Entity:

- Cochrane review: adding hyperthermia to standard RT or CCRT for **locally advanced cervical cancer** has an impact on **local tumor control, survival**, and **treatment related morbidity**.
- 6 RCTs in patients with primary cervical cancer **stage IIB, IIIB and IV**.

Treatment Modality:

- Conventional EBRT + brachytherapy, in one trial with Chemo as well.
- Patients were randomized into: RT
  RT + HT (3-12 treatments during EBRT)

- Patients recruitment sites: AMC Amsterdam using a device similar to the earlier designed BSD-1000, Erasmus MC Rotterdam used the BSD-2000 Hyperthermia device.

Cervix Cancer

Clinical Results:

- Majority of patients (74%) in the studies had FIGO **stage IIIB** cervical carcinoma.
- Treatment outcome : better for patients receiving RT+ HT
- Pooled data analysis yielded a significant:
  - higher complete response rate (RR 0.56; 95% CI 0.39-0.79; p<0.001),
  - reduced local recurrence rate at 3 years (HR 0.48; 95% CI 0.37-0.63; p<0.001),
  - better overall survival at 3 years (HR 0.67; 95% CI 0.45-0.99; p=0.05) after combined treatment.
- No significant difference was observed in
  - treatment related acute (RR 0.99; 95% CI 0.30-3.31; p=0.99) or
  - late grade 3-4 toxicity (RR 1.01; 95% CI 0.44-2.30; p=0.96) between the two treatment arms.

Cervix Cancer

Recurrent or Residual Disease

Addition of HT to chemotherapy increases response to >50% and 2 year survival to >10% in previously irradiated cervical cancer patients

	Study	HT	Chemotherapy	Outcome	Results
[17]	Phase II	HT 1 with each Cisplatin dose	Platinum based; 6 cycles	Objective Response (includes PR + CR)	58% with 16% 2yr survival
[18]	Phase II	HT+ChT: n=19 60 min, 1HT/wk	Cisplatin max 12 cycles	Response rate	50%
[19]	Phase II	HT+ChT: n=19 60 min, 1HT/wk	Platinum based; 6 cycles	Objective Response (PR and CR)	53%
[20]	Phase III RCT	mEHT+ChT: n=18, 3/wk (total 36); 60min	ChT: n=20, Platinum based; 4-7 cycles	Tumour response	mEHT+ChT: 50% CT: 20%; p=0.0461

[17] Franckena M et al. Weekly systemic cisplatin plus locoregional hyperthermia *Int J Hyperth*. 2007;23(5):443-450.
[18] Rietbroek RC et al. I*nternational Journal of Radiation Oncology Biology Physics*. 1996;34(4):887-893.
[19] de Wit R, et al. *British Journal of Cancer*. 1999;80(9):1387-1391.
[20] Lee S et . Treatment outcome analysis of chemotherapy combined with mEHT. *Oncology Letters*. 2017;14(1):73-78.

Breast Cancer

Locally Recurrent Breast Cancer (previously irradiated)

Meta-analysis of 34 studies, 2110 patients:

RT+HT = Complete response in >60% of patients

Median survival: 17 months, 3yr OS: 37% [21]

no other options

Hyperthermia is included in the National Comprehensive Cancer Network Guidelines as an option for breast cancer recurrences since 2015 [22]

Two Protocols : [23]

BVI: 8 x 4Gy (4 weeks) + 1HT/week

AM: 12 x 3Gy (3 weeks) + 2HT/week (less toxicity)

[21] Datta NR et al. *Int J of Rad Onc, Bio, Phys*. 2016,94(5):1073-1087
[22] Kouloulias V *et al*. *Breast Care*. 2015;10(2):109-116.
[23] Oldenborg S. et al. *Radiotherapy and Oncology*. 2015;117(2):223-228.

Esophageal Cancer

Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2017, **42**, 155–164 doi: 10.1111/jcpt.12498

Review Article

Chemoradiation combined with regional hyperthermia for advanced oesophageal cancer: a systematic review and meta-analysis

Y. Hu* MD, Z. Li†‡ PhD, D.-H. Mi†‡ PhD, N. Cao† MD, S.-W. Zu* MD, Z.-Z. Wen‡ MD, X.-L. Yu‡ MD and Y. Qu* PhD
**The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei Province , †The First Clinical Medical College of Lanzhou University, Lanzhou, Gansu Province, and ‡The Second People's Hospital of Gansu Province, Lanzhou, Gansu Province, China*

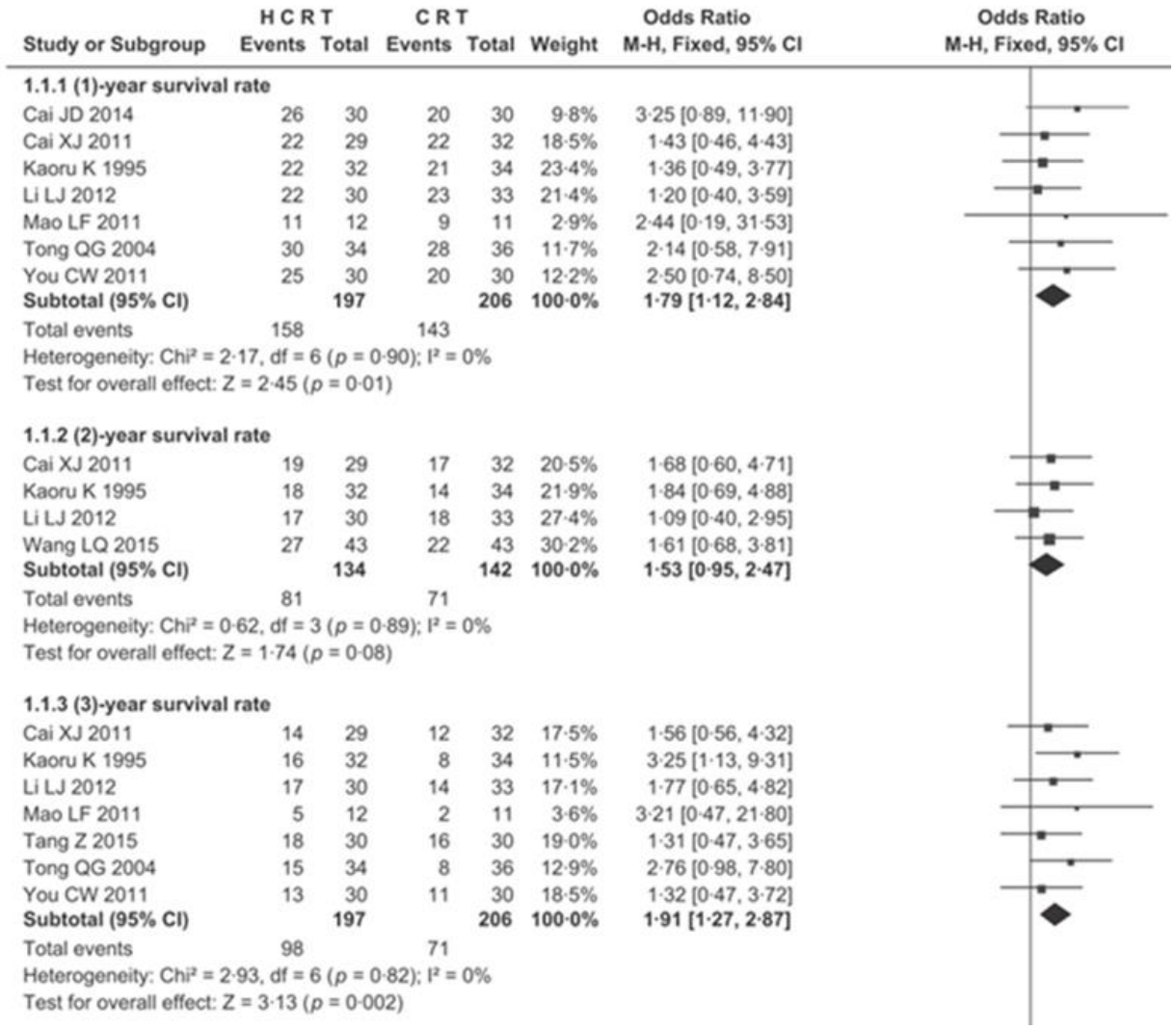
Received 9 September 2016, Accepted 29 November 2016

Keywords: **chemotherapy, hyperthermia, meta-analysis, oesophageal carcinoma, radiotherapy, randomized controlled trial, systematic review**

- **19 RCTs**
- **1519 patients**

Esophageal Cancer

- 19 RCTs
- 1519 patients



Study or Subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 (1)-year survival rate						
Cai JD 2014	26	30	20	30	9·8%	3·25 [0·89, 11·90]
Cai XJ 2011	22	29	22	32	18·5%	1·43 [0·46, 4·43]
Kaoru K 1995	22	32	21	34	23·4%	1·36 [0·49, 3·77]
Li LJ 2012	22	30	23	33	21·4%	1·20 [0·40, 3·59]
Mao LF 2011	11	12	9	11	2·9%	2·44 [0·19, 31·53]
Tong QG 2004	30	34	28	36	11·7%	2·14 [0·58, 7·91]
You CW 2011	25	30	20	30	12·2%	2·50 [0·74, 8·50]
Subtotal (95% CI)		**197**		**206**	**100·0%**	**1·79 [1·12, 2·84]**
Total events	158		143			
Heterogeneity: Chi² = 2·17, df = 6 (*p* = 0·90); I² = 0%						
Test for overall effect: Z = 2·45 (*p* = 0·01)						
1.1.2 (2)-year survival rate						
Cai XJ 2011	19	29	17	32	20·5%	1·68 [0·60, 4·71]
Kaoru K 1995	18	32	14	34	21·9%	1·84 [0·69, 4·88]
Li LJ 2012	17	30	18	33	27·4%	1·09 [0·40, 2·95]
Wang LQ 2015	27	43	22	43	30·2%	1·61 [0·68, 3·81]
Subtotal (95% CI)		**134**		**142**	**100·0%**	**1·53 [0·95, 2·47]**
Total events	81		71			
Heterogeneity: Chi² = 0·62, df = 3 (*p* = 0·89); I² = 0%						
Test for overall effect: Z = 1·74 (*p* = 0·08)						
1.1.3 (3)-year survival rate						
Cai XJ 2011	14	29	12	32	17·5%	1·56 [0·56, 4·32]
Kaoru K 1995	16	32	8	34	11·5%	3·25 [1·13, 9·31]
Li LJ 2012	17	30	14	33	17·1%	1·77 [0·65, 4·82]
Mao LF 2011	5	12	2	11	3·6%	3·21 [0·47, 21·80]
Tang Z 2015	18	30	16	30	19·0%	1·31 [0·47, 3·65]
Tong QG 2004	15	34	8	36	12·9%	2·76 [0·98, 7·80]
You CW 2011	13	30	11	30	18·5%	1·32 [0·47, 3·72]
Subtotal (95% CI)		**197**		**206**	**100·0%**	**1·91 [1·27, 2·87]**
Total events	98		71			
Heterogeneity: Chi² = 2·93, df = 6 (*p* = 0·82); I² = 0%						
Test for overall effect: Z = 3·13 (*p* = 0·002)						

CCRT + 熱療

在 1, 2, 3, 5, 7年存活比較好!

1.1.4 (5)-year survival rate						
Mao LF 2011	3	12	0	11	33·8%	8·47 [0·39, 185·35]
Tong QG 2004	8	34	1	36	66·2%	10·77 [1·27, 91·52]
Subtotal (95% CI)		**46**		**47**	**100·0%**	**9·99 [1·72, 57·91]**
Total events	11		1			
Heterogeneity: Chi² = 0·02, df = 1 (*p* = 0·90); I² = 0%						
Test for overall effect: Z = 2·57 (*p* = 0·01)						
1.1.5 (7)-year survival rate						
Mao LF 2011	2	12	0	11	50·6%	5·48 [0·23, 127·73]
Tong QG 2004	5	34	0	36	49·4%	13·61 [0·72, 256·28]
Subtotal (95% CI)		**46**		**47**	**100·0%**	**9·49 [1·14, 79·27]**
Total events	7		0			
Heterogeneity: Chi² = 0·18, df = 1 (*p* = 0·68); I² = 0%						
Test for overall effect: Z = 2·08 (*p* = 0·04)						

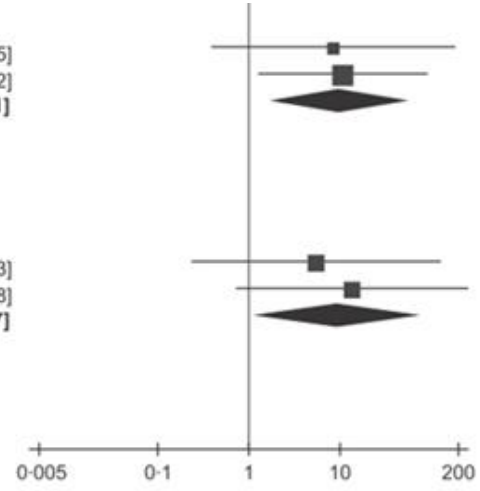


Fig. 2. Meta-analyses of OS rate for HCRT vs. CRT at 1, 2, 3, 5 and 7 years.

Head and Neck Stages II-IV

- **Meta-analysis by Datta et al in 2015 [26]**
  - **Six 2-armed studies; N= 451 patients (5 RCTs)**
  - **Complete response improved from 39.6% to 62.5% (OR 2.92; p < 0.0001)**
    - ✓ Nasopharyngeal
    - ✓ Oral Cavity
    - ✓ Oropharyngeal
    - ✓ Hypopharynx
    - ✓ Neck nodes
    - ✓ Recurrent laryngeal

- **2HT/week during EBRT (+- 12 HT treatments)**
- **With or without chemotherapy**



[26] Datta NR. *et al* (2015) Meta-analysis of HT and RT for head and neck cancers *Int J of Hyperthermia*. 2015;32(1):31-40.

Head and Neck Stages II-IV

Meta-analysis: Complete local response in head & neck (Datta *et al*, 2015):

RT (183/364, 50.3%) RT + HT (266/353, 75.3%), Odds ratio = 3.71 (95% CI, 2.55–5.38), $p < 0.001$

Ref	Patient characteristics	Treatment	CR / Total		Outcome	OR (95%CI)	p=
			No HT	HT			
[27]	NP (TNM II–IVA)	RT vs RT+ICHT	23/49	34/49	CR (radiological)	2.56 (1.12, 5.86)	***0.026***
[28]	NP (TNM III–IV)	CRT vs CRT+ICHT	49/78	62/76	CR	2.62 (1.25, 5.49)	***0.011***
[29]	NP (TNM I–IV)	RT vs RT+ICHT	73/90	86/90	CR (radiological)	5.01 (1.61, 15.55)	***0.005***
[30]	OC, OP, HP (TNM II–IV)	RT vs RT+HT	11/26	22/28	CR	5.00 (1.52, 16.46)	***0.008***
[31]	OP, HP	RT vs RT+HT	4/15	11/15	CR	7.56 (1.50, 38.15)	***0.014***
		Preop RT vs Preop RT+HT	4/24	10/18	CR (pathological)	6.25 (1.51, 25.86)	***0.011***
[32]	Neck nodes	RT vs RT+HT	9/22	15/18	CR	7.22 (1.61, 32.46)	***0.010***
[33]	Recurrent laryngeal	CRT vs CRT+HT	0/28	8/26	CR	26.19 (1.42, 481.51)	***0.028***
[34]	OC, OP (I–IV)	RT vs RT+HT	10/32	18/33	CR	2.64 (0.96, 7.28)	***0.061***

Abbreviations: CR: Complete response; CRT: Chemoradiotherapy; ICHT: Intracavity Hyperthermia; HP: Hypopharynx; NP: Nasopharyngeal; OC: Oral Cavity; OP: Oropharyngeal; OR: Odds Ratio; RT: Radiotherapy

[26] Datta NR. *et al* (2015) Meta-analysis of HT and RT for head and neck cancers *Int J of Hyperthermia*. 2015;32(1):31-40.

Bone Metastases

Phase III Trial on Pain Management for Bone Metastases[37]

- Exclusion: Pathologic fracture impending immediate surgical intervention, Pace maker in the treatment field
- Improves pain and local response from the 7% to 38% (*p*=0.006)
- Complete Response (CR) was defined as pain score 0 at the treated site with no concomitant increase in analgesic intake (oral morphine equivalent dose).

	HT:	EBRT:	Outcome	Results
RT+HT: n=29 **RT: n=28**	2/week after EBRT (total 4)	30Gy in 10 fractions	CR at 3 months Median time to pain progression after CR	RT+HT: 37.9% RT: 7.1%; p=0.006 RT+HT: n=>6mnths RT: n=55days; p<0.01

Abbreviations: CR: Complete Response; EBRT: External Beam Radiation; HT: Hyperthermia; RT: Radiation therapy

[35] Chi M-S *et al*., *International Journal of Radiation Onc, Bio, Phys.* 2017,100(1):78-87

Pancreatic Cancer

PANCREAS: locally advanced (IVA); metastatic; or refractory [39]

With Radiotherapy: HT 2/week (50-60Gy)
With Chemotherapy: On the same day and up to three times in between doses
ChT agents tested with HT: 5FU +/-MMC; Gem; Oxaliplatin; CDDP; Carboplatin

In a review including 14 trials:

HT may improve complete response (CR) from 35% to 44%
and median survival may be increased to up to 11.7 months

Trial type	patients	HT	RT and CHT	Outcome	Results
Review of 14 studies **With HT: n=248; Without HT: n=147**	Locally advanced: n=204(52%), metastatic: n=175(44%);	HT+RT: n=17 HT+CRT: n=82 RT+ChT: n=149	EBRT 50-60Gy ChT: 5FU; Gem; MMC; Oxali; CDDP; Carbop	CR Median Overall Survival: months	RT/ChT+HT: 43.9% RT/ChT: 35.3%; RT/ChT+HT: 11.7 RT/ChT: 5.6;

[37] van der Horst A *et al*. The clinical benefit of hyperthermia in pancreatic cancer: a systematic review, *International J Hyperthermia.* 2018,34(7):969-979

Sarcomas

Hyperthermia plus chemotherapy for soft tissue sarcomas

ESMO[40]: Irresectable, locally advanced high-risk STS (> or = 5 cm) grade 2 or 3 + RT/ChT OR combined with radiotherapy or chemotherapy for limb-preserving surgery;

Metastatic or recurrent tumours that have been previously exposed to treatment and require re-treatment.

Including Liposarcoma, leiomyosarcoma, synovial sarcoma.

Within two hours of each IV ChT OR HT 2/week + EBRT

	Patients	Treatment	Outcome	HT+ChT n=169	ChT n=172	P=
[41]	G2-G3, deep, >3cm STS	ChT: EIA x 8 cycles 3 wks apart	Progression free at 2yr	30%	19%	***0.035***
			Median PFS	120 months	75 months	***0.003***
			Median DFS	32 months	18 months	***0.011***
[42]		HT given on days 1 and 4 of each cycle, total 16 HT	5yr survival	63%	51%	***0.04***
			10yr Survival	53%	43%	
			Time to local progression	67.3 months	29.2 months	***0.002***
			Median survival	15.4yrs	6.2yrs	***0.04***

Abbreviations: ChT: chemotherapy; CR: Complete Response; EIA: etoposide, ifosfamide, and doxorubicin; STS: Soft tissue sarcoma; RT: Radiotherapy; HT: Hyperthermia; RAS: Radiation Associated Sarcoma

[40] ESMO – EURACAN Clinical Practice Guidelines for diagnosis, treatment Clinical Practice Guidelines. 2018;29(May).
[41] Issels RD *et al Lancet Oncology*. 2010;11(6):561-570.
[42] Issels R *et al JAMA Oncology*. 2018;4(4):483-492.

Re-Irradiation

Re-irradiation with HT offers a local response rate reported in over 50% of patients.

Hyperthermia (HT) in these cases is used in the absence of, or with limited, other options available.

HT 2/week during EBRT

- ✓ Breast Cancer[21]
- ✓ Recurrent laryngeal,[33]
- ✓ Recurrent rectal cancers,[38]
- ✓ Pancreatic cancer,[45]
- ✓ Radiation induced sarcomas,[48]
- ✓ Melanoma,[49]
- ✓ Glioblastomas,[50]

[21] Datta NR et al. *International Journal of Radiation Oncology, Biology, Physics*. 2016;94(5):1073-1087.
[33] Svetitsky P V. *The Journal of Laryngology & Otology*. 1990;104(9):704-705.
[38] Juffermans et al. *Cancer*. 2003;98(8):1759-1766.
[48] de Jong MAA et al. *Cancer.* 2012;118(1):180-187.
[45] Maluta S et al. *Strahlentherapie und Onkologie.* 2011;187(10):619-625.
[49] Overgaard J et al. *International Journal of Hyperthermia.* 1996;12(1):3-20.
[50] Heo J et al. *Neoplasma*. 2017;64(5):803-808.

Re-Irradiation

Summary of Studies on Re-Irradiation of Local Recurrences

	Tumour	Sample	RT	HT	Response
[21] Meta-analysis	Breast Cancer: Recurrent	34 studies, n=2110	BVI or AMC	BVI or AMC	CR at 3 months 60%
[33] Randomised	Laryngeal: Recurrent	HT group: n=26 Control: n=28 (all pts had methotrexate)	30Gy over 3 weeks	3/week	3year survival: 33% vs 0% 2 year survival: 75% vs 7%
[38] Phase II	Rectal: Recurrent	n=54	BVI or AMC	BVI or AMC	Palliative effect in 72%, duration 6 months
[45] non-randomised	Pancreas: Recurrent/ Metastatic	HT group: n=5 Control: n=7	30Gy in 10 fractions	2/week	Median survival: 15 vs 11 months (incl. metastatic dx)
[48] Retrospective	Radiation Associated Sarcoma (thorax)	n=16	32Gy in 8 fractions	2/week	Median survival: 15.5 months 75% response rate 44% CR
[49] Randomised	Melanoma: Recurrent/ Metastatic	HT group: n=9 Control: n=7	3 x 8/9Gy four days apart	With each RT	2yr local control: 28% vs 46%, p=0.008.
[50] Phase II	High Grade Gliomas: Recurrent	n=20	30Gy in 15 fractions	2/week	Median survival 8.4 months 6mnth survival: 67% 12mnth survival: 30%

Abscopal Effects

ORIGINAL RESEARCH ARTICLE

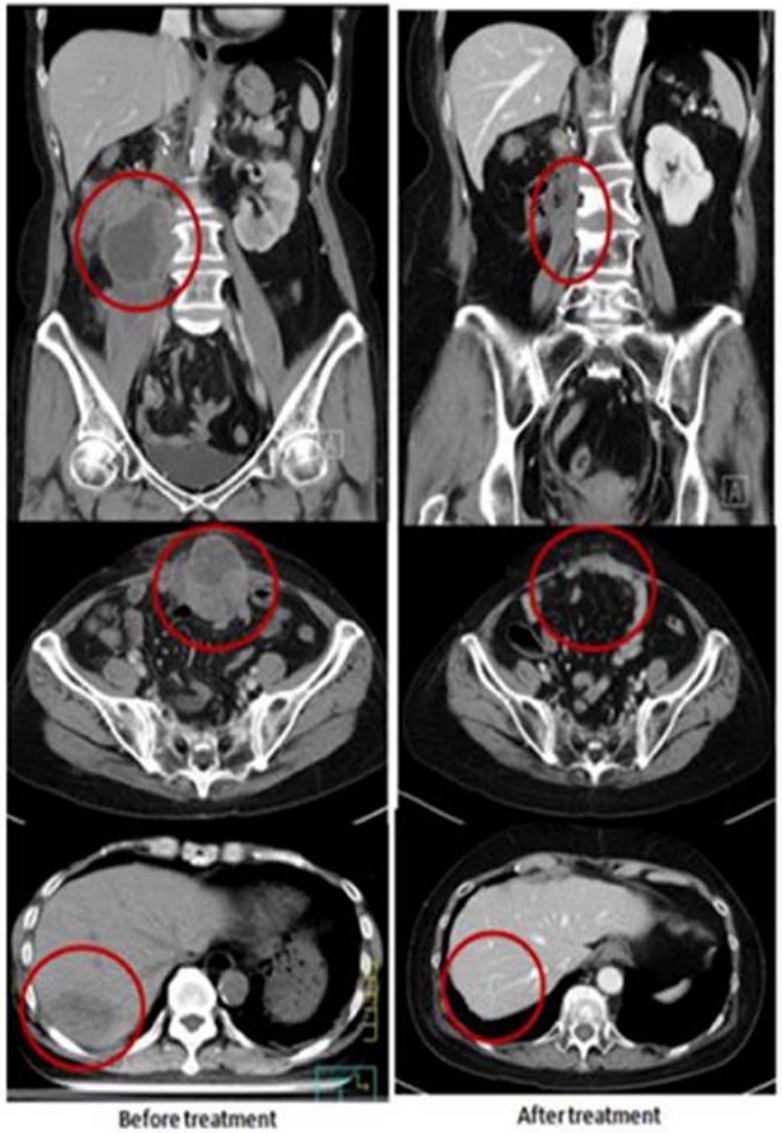
Front. Oncol., 10 March 2020 | https://doi.org/10.3389/fonc.2020.00254

Putative Abscopal Effect in Three Patients Treated by Combined Radiotherapy and Modulated Electrohyperthermia

Mau-Shin Chi[1,2], Minesh P. Mehta[3], Kai-Lin Yang[1,4], Hung-Chih Lai[5], Ying-Chu Lin[5], Hui-Ling Ko[1], Yu-Shan Wang[1,6], Kuang-Wen Liao[6] and Kwan-Hwa Chi[1,7*]

A 60-year-old female had right renal pelvis urothelial carcinoma diagnosed in October 2016. She underwent robotic right nephroureterectomy and bladder cuff excision, revealing a pT4N0 tumor treated with adjuvant tumor bed radiotherapy to 48 Gy in 24 fxs

2nd course RT: 40Gy/20 + mEHT x5 weekly +Carbo+Gemzer x2



慢 性 疾 病 的 應 用

- 慢性攝護腺炎 Chronic Prostatitis
- 慢性骨盆炎 Chronic pelvic inflammatory disease
- 關節炎 Arthritis
- 缺血性關節壞死　Avascular necrosis
- 肩周炎
- 每次30-35分鐘,　10次為一療程，一星期五次,關閉 modulation

電熱療總結(1):

- 改善腫瘤血流及缺氧 →加強化療、放療、化放療、免疫治療的功效
- 加熱→抑制癌細胞因放療破壞了的DNA修復，癌細胞較容易凋亡
- 改善腫瘤微環境→透過熱休克蛋白(HSP70)誘發自身免疫力以打擊癌細胞

電熱療總結(2):

在標準療法如 Chemo, RT, CCRT,或 immunotherapy，加入電熱療可增加臨床療效:

- ✓ Overall Survival
- ✓ Local control
- ✓ Distant mets rate
- ✓ PFS
- ✓ DFS
- ✓ Quality of life

✓很少副作用, 約 2% 感覺有點燙

✓沒有累積熱毒性!

✓對於沒空間(或拒絕)放療或化療的病人，提供最好的另類選擇

- ✓如肝、腎功能不好
- ✓放療劑量已滿
- ✓化療毒性太大

電熱治療

安全、有效、治療輕鬆、

無累積毒性、很少副作用

Acknowledgement :

- Yu-Shan Wang Ph.D.,
- Prof. Kwan Hwa Chi, and the collaboration team members.



THANK YOU
FOR
YOUR ATTENTION

References

1. Dewhirst MW et al. Re-setting the biologic rationale for thermal therapy. *Int J Hyperth*. 2005;21(8):779-790.

2. Oei AL et al. Effects of hyperthermia on DNA repair pathways: One treatment to inhibit them all. *Radiat Oncol*. 2015;10(1):1-13.

3. Toraya-Brown S et al. Local tumour hyperthermia as immunotherapy for metastatic cancer. *Int J Hyperth*. 2014;30(8):531-539.

4. Nishida T et al. Correlation between cell killing effect and cell membrane potential after heat treatment: analysis using fluorescent dye and flow cytometry. *Int J Hyperth*. 1997;13(2):227-234.

5. van der Zee J. Heating the patient : a promising approach ? *Ann Oncol*. 2002;13(8):1173-1184.

6. Pandita TK et al. Molecular Parameters of Hyperthermia for Radiosensitization. *Crit Rev Eukaryote Gene Expr*. 2009;19(3):235-251.

7. Datta NR et al. Local hyperthermia combined with radiotherapy and- / or chemotherapy : Recent advances and promises for the future. *Cancer Treat Rev*. 2015;41(9):742-753.

8. Mallory M et al. Therapeutic Hyperthermia: The old, the new, and the upcoming. *Crit Rev Oncol Hematol*. 2016;97:56-64.

9. van der Zee J et al. The Dutch Deep Hyperthermia trial: Results in cervical cancer. *Int J Hyperth*. 2002;18(1):1-12.

10.Franckena M et al. Long-Term Improvement in Treatment Outcome After Radiotherapy and Hyperthermia in Locoregionally Advanced Cervix Cancer: An Update of the Dutch Deep Hyperthermia Trial. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1176-1182.

11.Harima Y et al. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *Int J Hyperth*. 2009;25(5):338-343.

12.Vasanthan A et al. Regional hyperthermia combined with radiotherapy for uterine cervical cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency. *Int J Radiat Oncol Biol Phys*. 2005;61(1):145-153.

13.Westermann AM et al. First Results of Triple-Modality Treatment Combining Radiotherapy, Chemotherapy, and Hyperthermia for the Treatment of Patients with Stage IIB, III, and IVA Cervical Carcinoma. *Cancer*. 2005;104(4):763-770.

14.Harima Y et al. A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer. *Int J Hyperth*. 2016;32(7):801-808.

15. Minnaar CA et al. The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa : Early results from a phase III randomised controlled trial. *PLoS One*. 2019;14(6):e0217894.

16. Datta NR et al. Hyperthermia and radiotherapy with or without chemotherapy in locally advanced cervical cancer: a systematic review with conventional and network meta-analyses. *Int J Hyperth*. 2016;32(7):809-821.

17. Franckena M et al. Weekly systemic cisplatin plus locoregional hyperthermia : An effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area. *Int J Hyperth*. 2007;23(5):443-450.

18. Rietbroek RC et al. Feasibility, toxicity, and preliminary results of weekly loco-regional hyperthermia and cisplatin in patients with previously irradiated recurrent cervical carcinoma or locally advanced bladder cancer. *Int J Radiat Oncol Biol Phys*. 1996;34(4):887-893.

19. de Wit R et al. A phase I/II study of combined weekly systemic cisplatin and locoregional hyperthermia in patients with previously irradiated recurrent carcinoma of the uterine cervix. *Br J Cancer*. 1999;80(9):1387-1391.

20. Lee S et al. Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation. *Oncol Lett*. 2017;14(1):73-78.

21. Datta NR et al. Hyperthermia and Radiation Therapy in Locoregional Recurrent Breast Cancers: A Systematic Review and Meta-analysis. *Int J Radiat Oncol Biol Phys*. 2016;94(5):1073-1087.

22. Kouloulias V et al. Hyperthermia is now included in the NCCN clinical practice guidelines for breast cancer recurrences: An analysis of existing data. *Breast Care*. 2015;10(2):109-116.

23. Oldenborg S et al. Reirradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: Size matters. *Radiother Oncol*. 2015;117(2):223-228.

24. Linthorst M et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: Results in 248 patients. *Radiother Oncol*. 2015;117(2):217-222.

25. Vernon CC et al. Radiotherapy with or without hyperthermia for superficial breast cancer: Results from give randomized controlled trials. *Int J Radiat Oncol Biol Phys*. 1996;35(4):731-744.

26. Datta NR et al. Hyperthermia and radiotherapy in the management of head and neck cancers: A systematic review and meta-analysis. *Int J Hyperth*. 2015;32(1):31-40.

27. Wen Q-L et al. Comparing Radiotherapy with or without Intracavitary Hyperthermia in the Treatment of Primary Nasopharyngeal Carcinoma: A Retrospective Analysis. *Tumori J*. 2014;100(1):49-54.

28. Kang M et al. Long-term efficacy of microwave hyperthermia combined with chemoradiotherapy in treatment of nasopharyngeal carcinoma with cervical lymph node metastases. *Asian Pacific J Cancer Prev*. 2013;14(12):7395-7400.

29. Hua Y et al. Intracavity hyperthermia in nasopharyngeal cancer: A phase III clinical study. *Int J Hyperth*. 2011;27(2):180-186.

30. Huilgol NG et al. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer : A report of randomized trial. *J Cancer Res Ther*. 2010;6(4):492-496.

31. Hiraki Y et al. Effectiveness of RF capacitive hyperthermia combined with radiotherapy for Stages III and IV oro-hypopharyngeal cancers : A non-randomized comparison between thermoradiotherapy and radiotherapy. *Int J Hyperth*. 2015;14(5):445-457.

32. Valdagni R et al. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymphnodes in stage IV head and neck patients. *Int J Radiat Oncol Biol Phys*. 1993;28(1):163-169.

33. Svetitsky P V. Effect of mircowave and ionizing radiation in patients with recurrent laryngeal carcinoma. *J Laryngol Otol*. 1990;104(9):704-705.

34. Datta NR et al. Head and neck cancers: results of thermoradiotherapy versus radiotherapy. *Int J Hyperth*. 1990;6(3):479-486.

35. Chi MS et al. Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial. *Int J Radiat Oncol Biol Phys*. 2017;100(1):78-87.

36. Overgaard J et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. *Lancet Oncol*. 1995;345(8949):540-543.

37. van der Horst A et al. The clinical benefit of hyperthermia in pancreatic cancer: a systematic review. *Int J Hyperth*. 2018;34(7):969-979.

38. Juffermans JHM et al. Reirradiation and Hyperthermia in Rectal Carcinoma A Retrospective Study on Palliative Effect. *Cancer*. 2003;98(8):1759-1766.

39. Li Z et al. The efficacy of radiofrequency hyperthermia combined with chemotherapy in the treatment of advanced ovarian cancer. *Open J Med*. 2018;13:83-89.

40. Casali P et al. Soft tissue and visceral sarcomas : ESMO – EURACAN Clinical Practice Guidelines for diagnosis , treatment Clinical Practice Guidelines. *ESMO Clin Pract Guidel*. 2018;29(May).

41. Issels RD et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma : a randomised phase 3 multicentre study. *Lancet Oncol*. 2010;11(6):561-570.

42. Issels R et al. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma. *JAMA Oncol*. 2018;4(4):483-492.

43. Longo TA et al. A systematic review of regional hyperthermia therapy in bladder cancer. *Int J Hyperth*. 2016;32(4):381-389.

44. van Driel WJ et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. *N Engl J Med*. 2018;378(3):230-240.

45. Maluta S et al. Regional hyperthermia combined with chemoradiotherapy in primary or recurrent locally advanced pancreatic cancer: An Open-Label Comparative Cohort Trial. *Strahlentherapie und Onkol*. 2011;187(10):619-625.

46. Klimanov MY et al. Efficacy of Combined Regional Inductive Moderate Hyperthermia and Chemotherapy in Patients With Multiple Liver Metastases From Breast Cancer. *Technol Cancer Res Treat*. 2018;17:Article no. 1533033818806003.

47. Yu J Il et al. Prospective phase II trial of regional hyperthermia and whole liver irradiation for numerous chemorefractory liver metastases from colorectal cancer. *Radiat Oncol J*. 2016;34(1):34-44.

48. de Jong MAA et al. Reirradiation and Hyperthermia for Radiation-Associated Sarcoma. *Cancer*. 2012;118(1):180-187.

49. Overgaard J et al. Hyperthermia as an adjuvant to radiation therapy of recurrent or metastatic malignant melanoma. A multicentre randomized trial by the European Society for Hyperthermic Oncology. *Int J Hyperth*. 1996;12(1):3-20.

50. Heo J et al. Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas. *Neoplasma*. 2017;64(5):803-808.

51. Szasz A et al. Electro-hyperthermia: a new paradigm in Cancer Therapy. *Dtsch Zeitschrift fur Onkol*. 2001;33(3):91-99.

52. Fiorentini G et al. Hyperthermia today: Electric energy, a new opportunity in cancer treatment. *J Cancer Res Ther*. 2006;2(2):41-46.

53. Jossinet J. The impedivity of freshly excised human breast tissue. *Physiol Meas*. 1998;19(1):61-75.

54. Papp E et al. Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (mEHT). *Open J Biophys*. 2017;7:216-229.

55. Szasz O et al. Hyperthermia Dosing and Depth of Effect. *Open J Biophys*. 2018;8(1):31-48.

56. Kroesen M et al. The Effect of the Time Interval Between Radiation and Hyperthermia on Clinical Outcome in 400 Locally Advanced Cervical Carcinoma Patients. *Front Oncol*. 2019;9(134):1-11.

57. van der Zee J et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. *Lancet*. 2000;355(9210):1119-1125