Tumor-directed immunotherapy: combined radiotherapy and oncothermia

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www.oncothermia-journal.com/journal/2018/Tumor_directed_immunotherapy.pdf

Tumor-directed immunotherapy: combined radiotherapy and oncothermia

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Professor, National Yang-Ming University

Objective
Radiotherapy is an important part of cancer treatment. Hyperthermia has long been regarded as one of the best radiosensitization method. Oncothermia is a new kind of hyperthermia machine emphasizing energy absorbed on tumor cell membrane instead of nonspecific temperature rising around the treatment region. We proposed that oncothermia may have immune potentiation effect besides its radio(chemo)-sensitization effect

Methods
We aimed to examine, how real the abscopal events and what is the therapeutic effect of combined oncothermia and RT. Patients treated with combined RT and oncothermia since January 2017 till December 2017 at Shin-Kong Hospital, Taipei were retrospectively reviewed. We analyzed those who have measurable disease, performance status ≦ 2, a minimal RT dose of 30Gy and at least 4 times of oncothermia treatments. The primary prostate cancers were excluded.

Results
There were 60 patients evaluable, 27 patients with localized disease, in whom RT were the main treatment. Among them the CR rate was 22.2%, PR rate was 55.5%, SD with 14.8%. Two patients (one phylloid tumor of breast and one pancreatic cancer) were progressive disease after treatment. Most patients had acceptable local control for a median follow-up time of 9 months. Thirty-three patients with metastatic disease received palliative RT for a total of 38 sites, with a median dose of 44Gy/22fx to major disease sites. Patients with CR/PR has much longer survival than those not (SD+PD) ($P<0.001$). Shallower tumor (<5cm below skin) seemed to have batter effect than deeper tumor, but not significant ($P>0.1$). The objective response (CR+PR) in treated area is 60.7%. Most strikingly, there were obvious abscopal response in 3 patients. All of them had autoimmune reaction from treatment. One patient had autoimmune hepatitis the other one had dermatitis hapefiforms, and one patient had severe myasthenia gravis. They all had long duration of response without systemic treatment.

Conclusion
We reported that the combination of RT and oncothermia is effective and well tolerated. Oncothermia seems to have efficient radiosensitization effect in combined with RT or CCRT. Only randomized trial can answer the real clinical benefit of combined RT+HT on advanced cancer. However, a connection of autoimmune response is an evidence of immune boosting from oncothermia. Oncothermia activates lymphocyte in situ and provoked abscopal effect with RT. How oncothermia treatment provokes autoimmune reaction can pave the way antitumor immunity is underway

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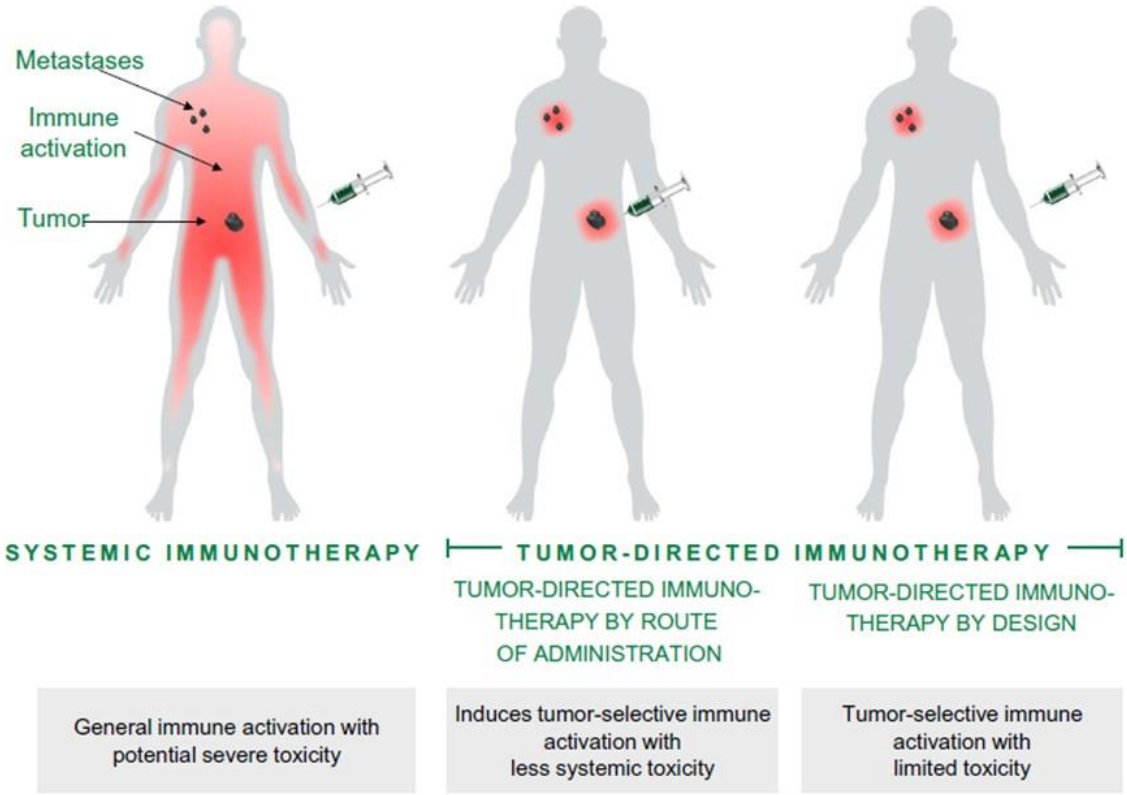
Shin-Kong Memorial Hospital, Taipei

Tumor-directed immunotherapy

- Produce specific immune cells that did not exit.
- Activate immune cells that have already home to the tumor/ local LN where tumor antigen present.
- Minimizing irrelevant activation of the rest of immune system.

Cancer Immunol Immunother Published online: 06 October 2016



Goal of in situ vaccination

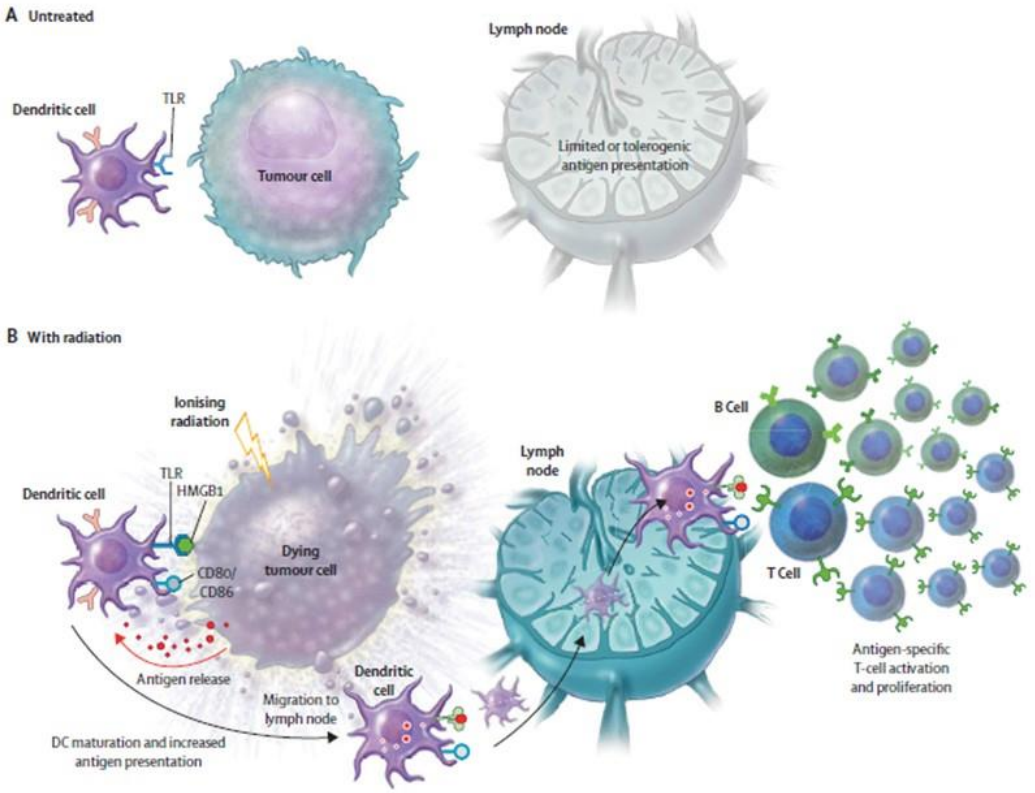
- Stimulate local anti-tumor immune response
- Generate systemic anti-tumor immune response
- Local control + systemic control

- Immune system is inherently systemic, Not local!
- But local inflammation is much safer than systemic inflammation, if the inflammation should be strong enough.

Methods of in situ vaccination

- Cell death + immune adjuvant (local)
- Tumor targeted immunotherapy
- The role of RT
- The role of HT

Lancet Oncology 2015:
16: e498–509



7

STING

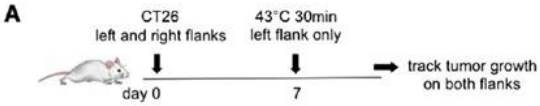
- The most important source of STING is endothelial cells.
- The principle controlling source is cyclic GMP-AMP synthase (cGAS)-the cytosolic DNA sensor for STING.
- cGAS STING-IFN is required for DCs cross-priming.
- DNA delivery in a cell contact – dependent manner to DC-tumor interaction.
- Exogenous cGAMP could improve RT effect effectively.

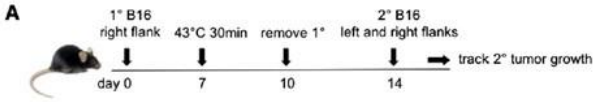
8

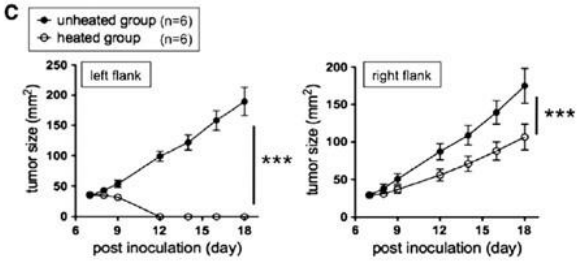
Local hyperthermia treatment of tumors induces CD8$^+$ T cell-mediated resistance against distal and secondary tumors

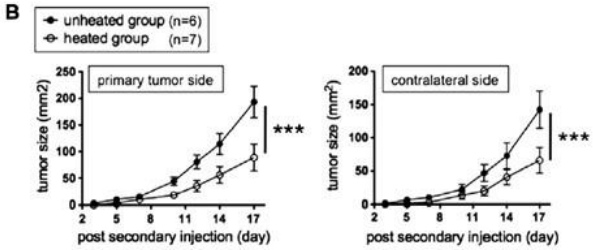
Seiko Toraya-Brown, PhD[a,1], Mee Rie Sheen, MS[a,1], Peisheng Zhang, MD[a], Lei Chen, BS[a],

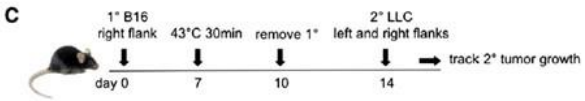
Nanomedicine: Nanotechnology, Biology, and Medicine
10 (2014) 1273 – 1285

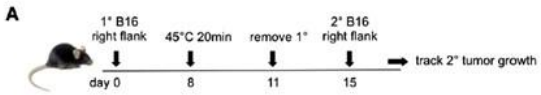


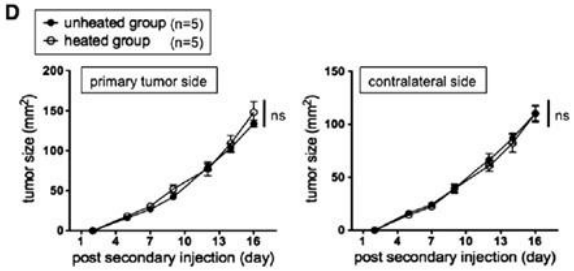


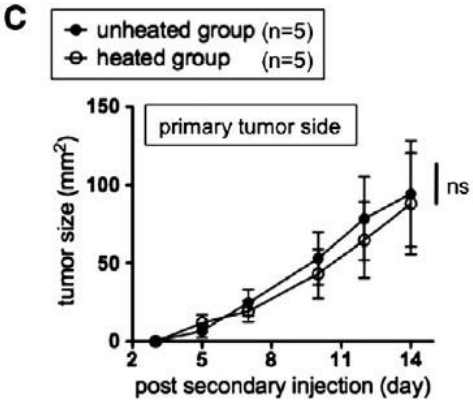


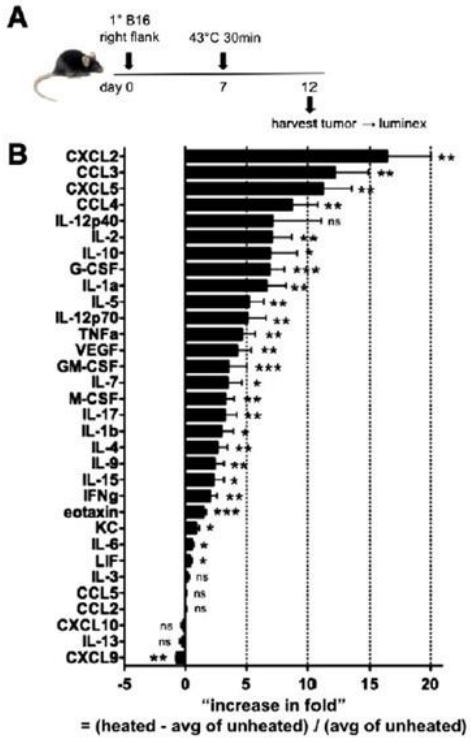


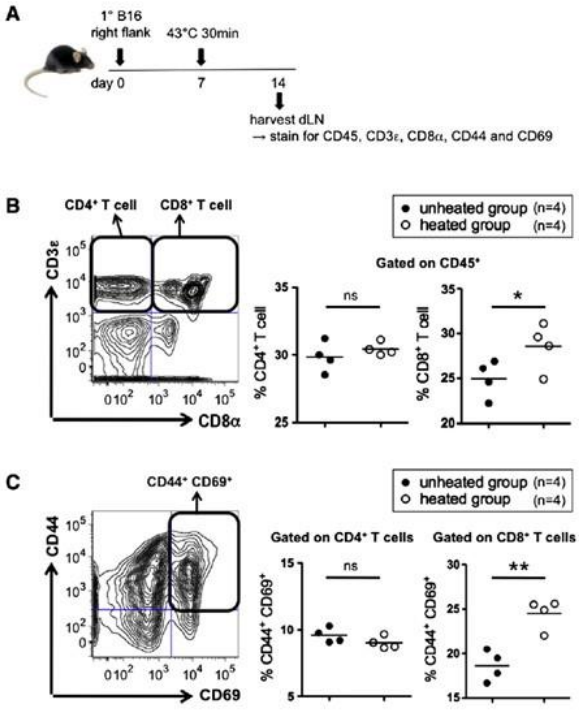












SKH-Hyperthermia Center

Oncothermia EHY-2000

Yamamoto RF-8

Thermatron RF-8 vs Oncothermia

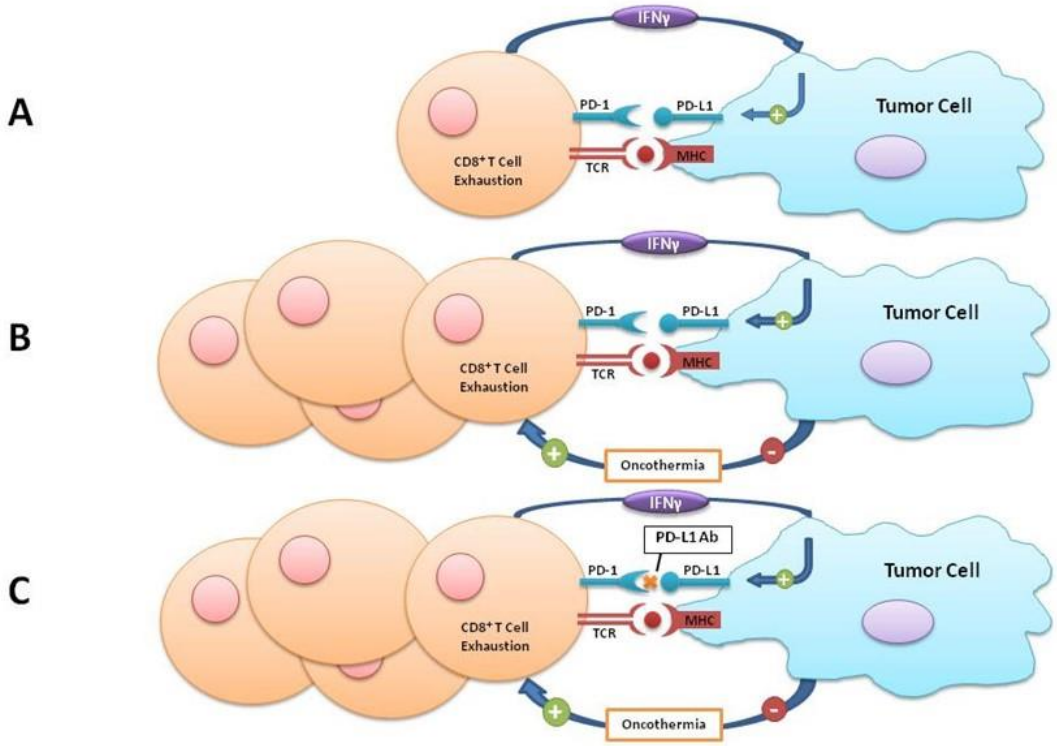
- Both are RF hyperthermia (8MHz vs 13.56 MHz), but different in electrode (capacitive vs radiative capacitive)
- RF-8 maximizing the power to heat, Oncothermia maximizing current (minimizing voltage) with fixed power.
- Oncothermia uses SAR, based on Joule energy absorption for dose; RF-8 uses CEM43Tx, based on temperature.
- The goal of RF-8 is the homogeneous heating of tumor mass, while oncothermia goal is the heterogeneous heating of the membrane rafts of malignant cells.

RF-8 is a more reliable temperature dependent radio(chemo)sensitization machine, but Oncothermia has more Immune sensitization effect.

Why? Really?

Oncothermia is a hyperthermia machine with stronger excitability than heat

1. Cancer cells were excited but exhausted with ATP depletion.
2. Immune cells were excited and activated

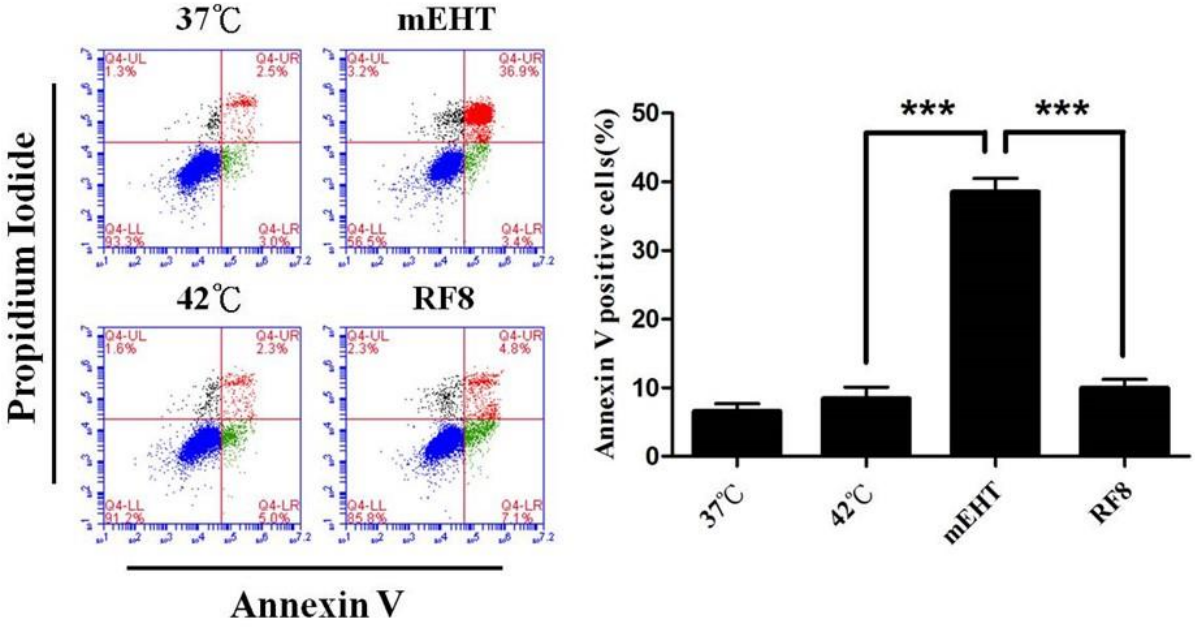


The rational for adding Anti PD-L1 monoclonal antibody to Oncothermia

Oncothermia as immunotherapy machine ?

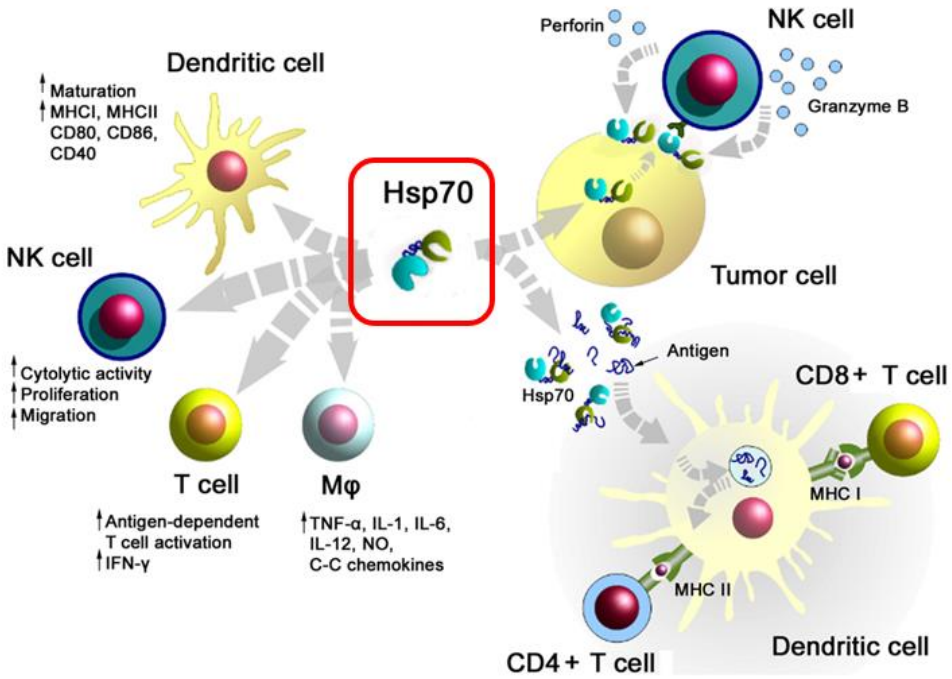
- **Will oncothermia change tumor microenvironment ?**
- **Will oncothermia activate immune cells ?**
- **Will oncothermia intensify the effect of immune checkpoint inhibitors ?**
- **Will oncothermia increase abscopal effect ?**
- **Will oncothermia increase autoimmune reaction ?**
- **Will oncothermia produce tumor hyperprogression ?**

Significant Elevation of Apoptosis After Oncothermia Treatment



Yang KL et al, Oncotarget. 2016 Dec 20;7(51):84082-84092.

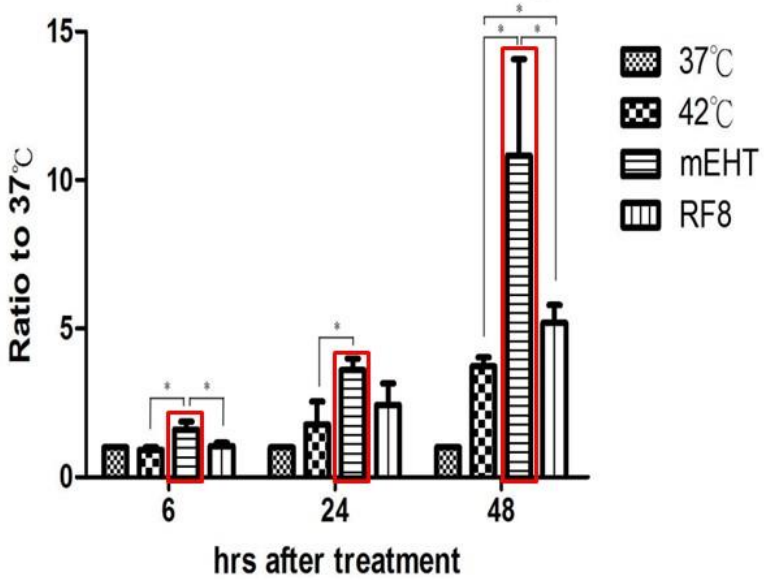
Major immune modulatory functions of heat shock protein 70 (Hsp70)



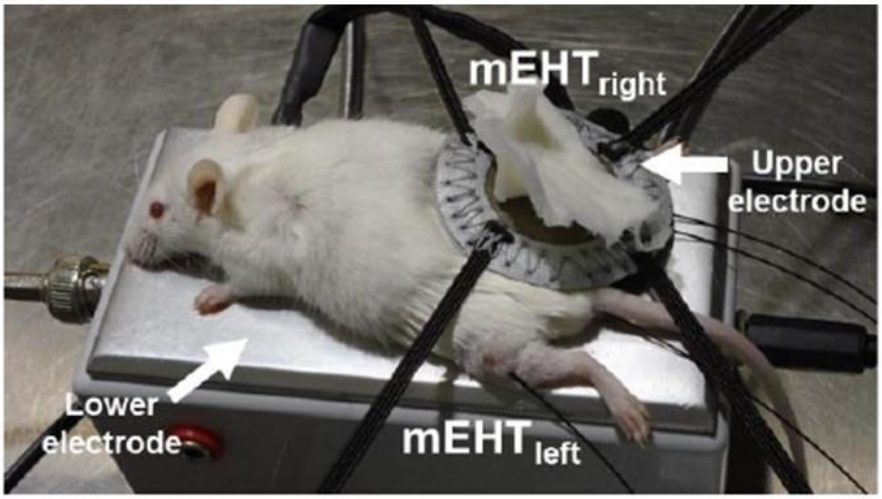
Shevtsov M and Multhoff G (2016) *Front. Immunol.* 7:171.

Stress protein analysis

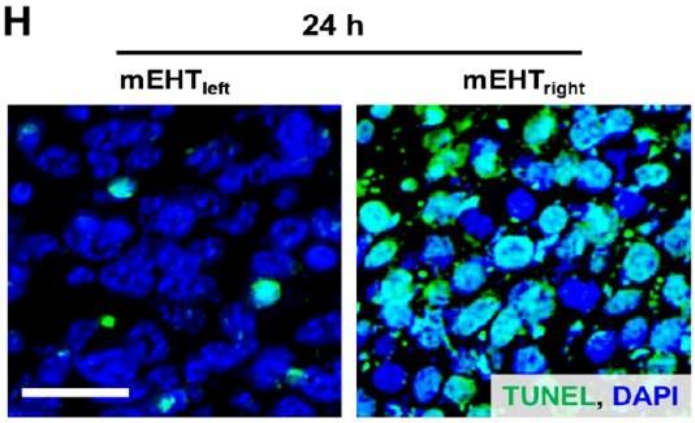
The release of HSP70 expression



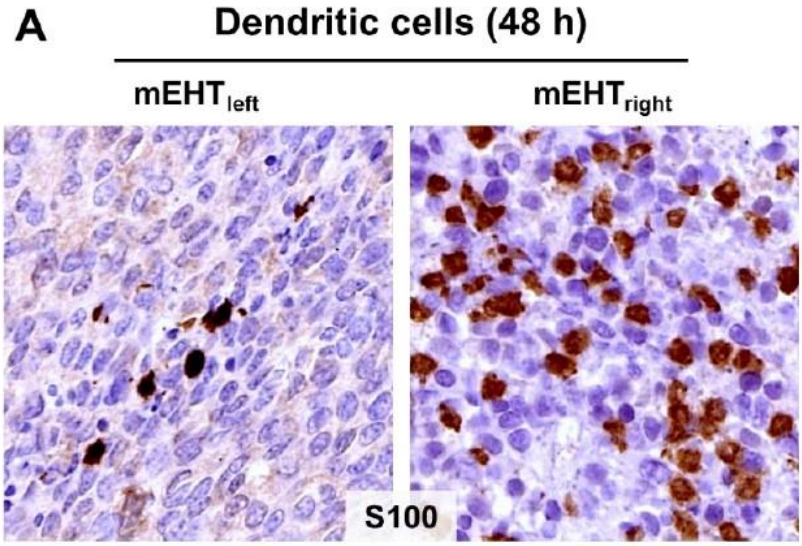
Oncothermia triggered a significantly secretion of HSP70 from cancer cells.



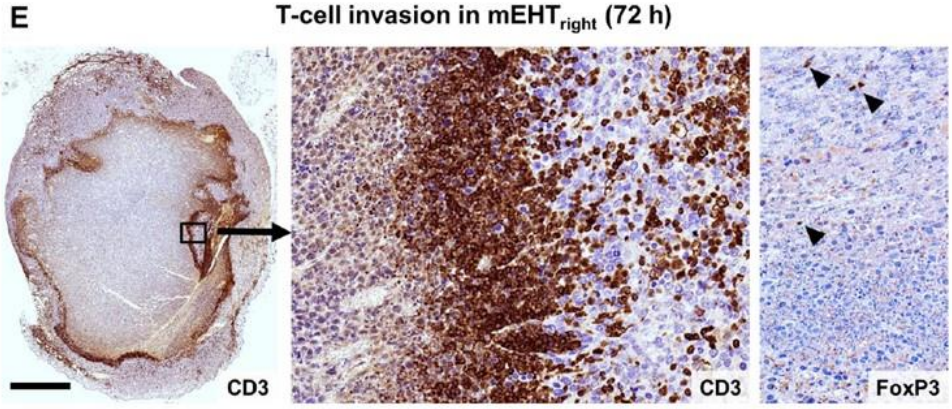
Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts
Vancsik T, Krenacs T, et al. 2018



Vancsik T, Krenacs T, et al. 2018

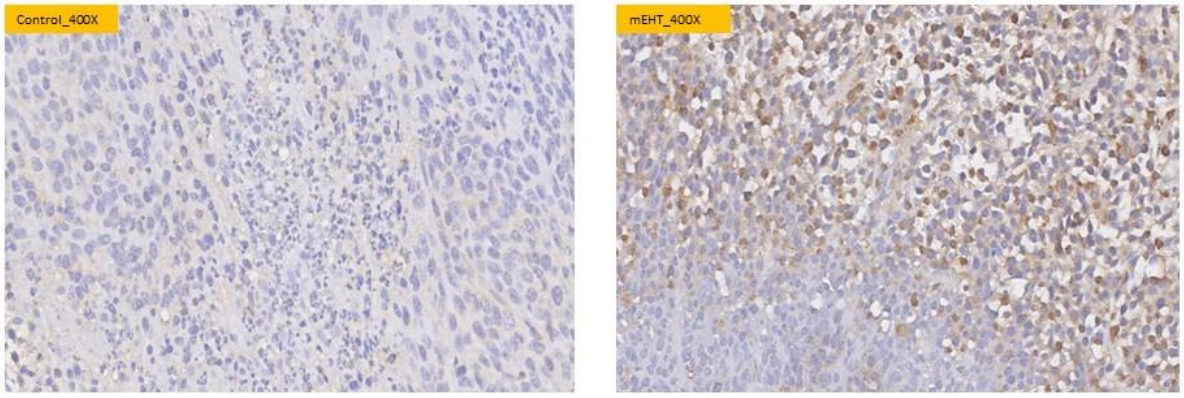


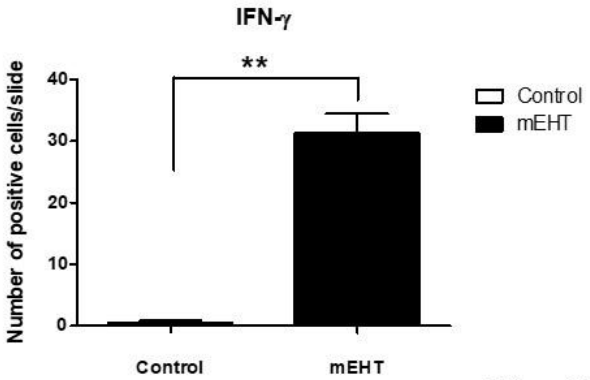
Vancsik T, Krenacs T, et al. 2018



Vancsik T, Krenacs T, et al. 2018

Oncothermia Induced IFN-γ Production in Tumor





Wang YS et al, Unpublished data

Oncothermia as immunotherapy machine ?

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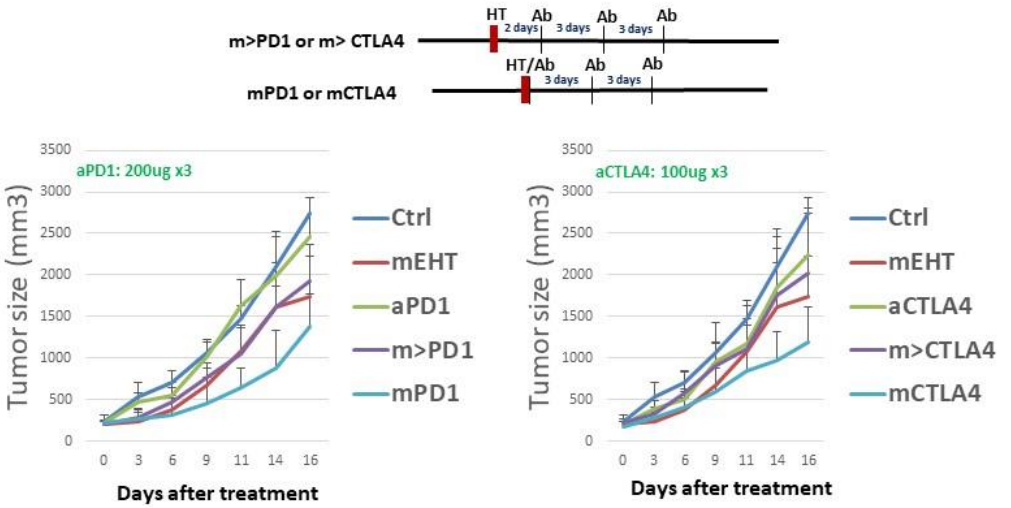


Ctrl: n=7, mEHT: n=6, aPD1: n=8, m>PD1: n=4, mPD1:n=4, aCTLA4:n=6, m>CTLA4: n=4, mCTLA4: n=4

mEHT: 42°C, 30min

T-test

Ctrl vs mEHT	Ctrl vs aPD1	Ctrl vs mPD1	Ctrl vs m>PD1	mEHT vs mPD1	mEHT vs m>PD1
0.000643412	0.279057606	0.000021	0.002460701	0.273198325	0.622015698
	Ctrl vs aCTLA4	Ctrl vs mCTLA4	Ctrl vs m>CTLA4	mEHT vs mCTLA4	mEHT vs m>CTLA4
	0.028418172	0.000013	0.039724289	0.131244518	0.561856883

Retrospective review of our Oncothermia experience:

- Treatment period: 2017/1- 2017/11.
- All patients were treated with combined radiotherapy and oncothermia with or without other systemic therapy.
- Response was evaluated on irradiated site

Patient characteristics

Characteristics	No	%
Sex		
Female	26	43.3
Male	34	56.7
Age, median, range	59.5	36-89
WHO Performance status		
0	1	1.7
1	54	90.0
2	5	8.3
Localized disease	27	
RT	27	100
CT	17	63.0
IO	1	3.7
CT+IO	2	7.4
Metastatic/ Recurrent disease	33	
RT	33	100
CT	12	36.4
IO	8	24.2
CT+IO	8	24.2

Cancer Type

Primary cancer site	Localized(N=27)	(%)	Metastatic/ Recurrent(N=33)	(%)
Breast ca	6	22.2	7	21.2
Lung ca	5	18.5	5	15.2
HCC	4	14.8	3	9.1
Head &Neck ca	2	7.4	2	6.1
Pancreas ca	2	7.4	1	3.0
Cholangiocarcinoma	1	3.7	3	9.1
Bladder ca	1	3.7	2	6.1
Colon ca	1	3.7	2	6.1
Esophageal ca	1	3.7	1	3.0
GBM	1	3.7	0	0
Thyroid ca	1	3.7	0	0
Spine tumor	1	3.7	0	0
Gallbladder ca	1	3.7	0	0
Prostate ca	0	0	1	3.0
Gastric ca	0	0	1	3.0
Cervix cancer	0	0	1	3.0
Ovary ca	0	0	1	3.0
Rectal ca	0	0	1	3.0
Urothelic cancer	0	0	1	3.0
Uterine sarcoma	0	0	1	3.0

Response rate on the irradiated sites

Response	Localized(N=27)		Metastatic/ Recurrent(N=33)	
CR	6 (22.2%)	77.7%	2 (6.1%)	60.7%
VGPR*	5 (18.5%)		5 (15.2%)	
PR	10 (37.0%)		13 (39.4%)	
SD	4 (14.8%)		9 (27.3%)	
PD	2 (7.4%)		4 (12.1%)	

*VGPR = Very good CR , mean >90% shrinkage

Response rate according to tumor size analysis for all patients

Tumor volume	CR/PR (%)	SD/PD(%)
GTV≧500cm³ (N=12)	11 (91.7)	1 (8.3)
GTV＜500cm³ (N=48)	30 (62.5)	18 (37.5)

P=0.049*

Treatment toxicity (CTCAE v4.0)

Toxicity	Case number (N)	Grade
Skin toxicity	1*	1
Hepatic toxicity	1*	3
Myelotoxicity	0	0
Neurotoxicity	1*	3
Renal toxicity	0	0
Pneumonitis	0	0
Soft tissue damage	0	0
Fatigue	0	0
Fever	0	0
Fat induration	0	0

*auto-immune reaction

許*毓 Hepatoma

2016/10/16 治療前CT

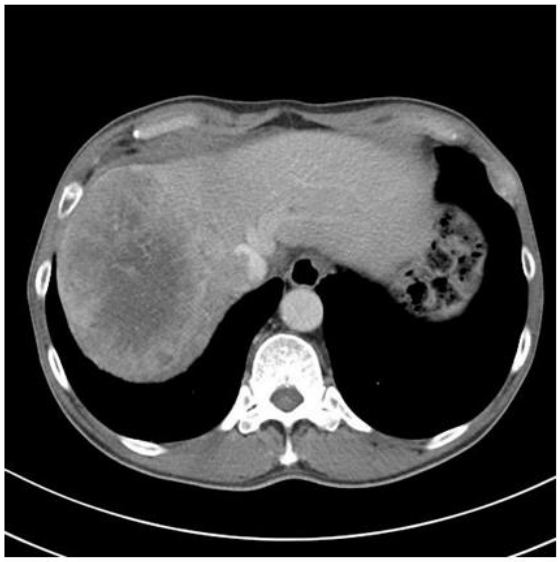
20170525治療後CT

王*豪 Cholangiocarcinoma

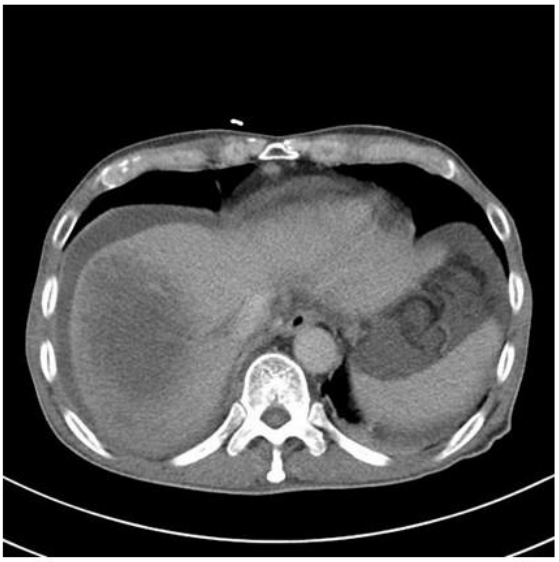
20170608治療前CT

20170731治療中CT

曾*耀 Hepatoma

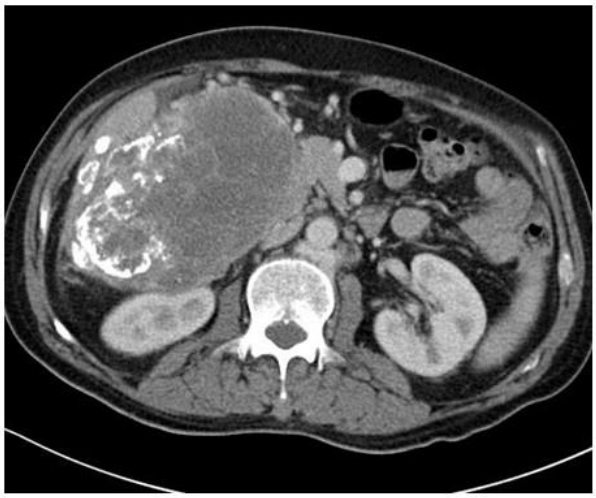


20161201治療前CT

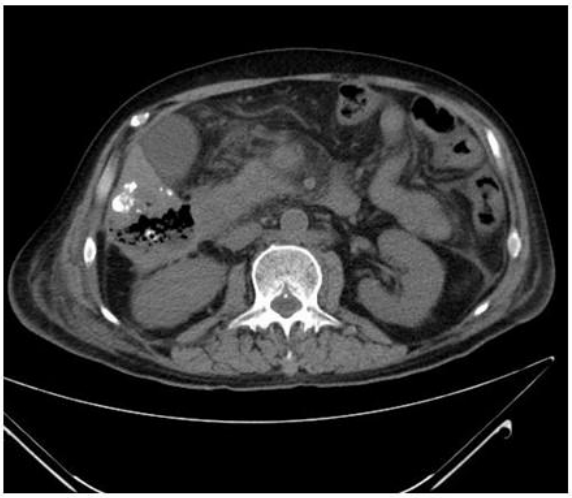


20170216最後一天治療完CT

郭*豪 14530953



20170425治療前CT



20170707 治療第一階段完CT

許*欣 Hepatoma

20171009治療前CT

20180403治療後CT

鄭*玲05537437

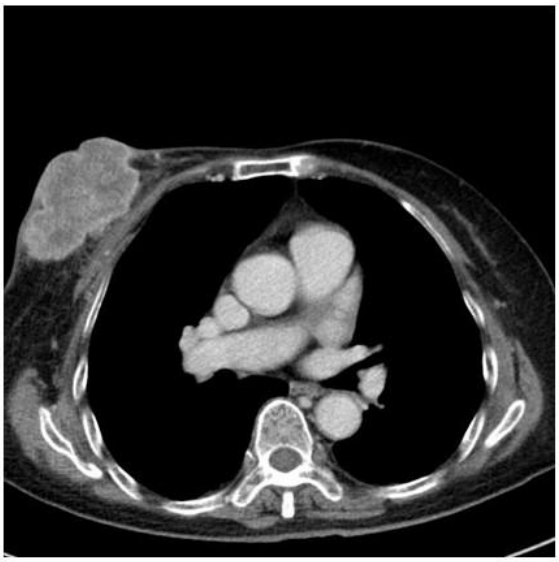
治療前

治療後

陳*鳳 20067028

20170328治療前CT　　20171024治療後CT　　20171226治療後 追蹤CT

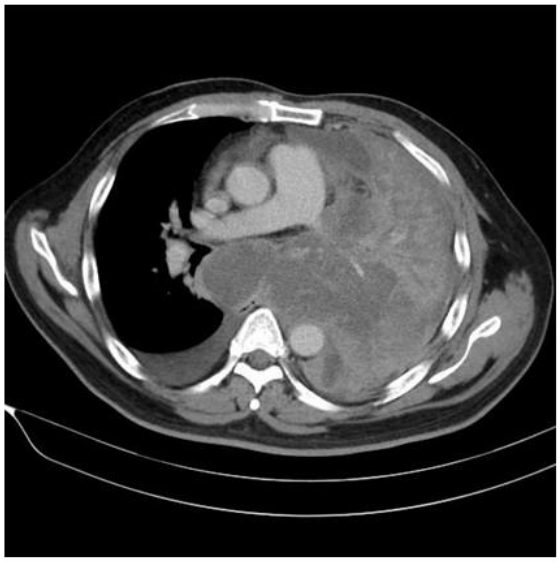
簡*妙子 Breast ca



20161206治療前

20171017治療後

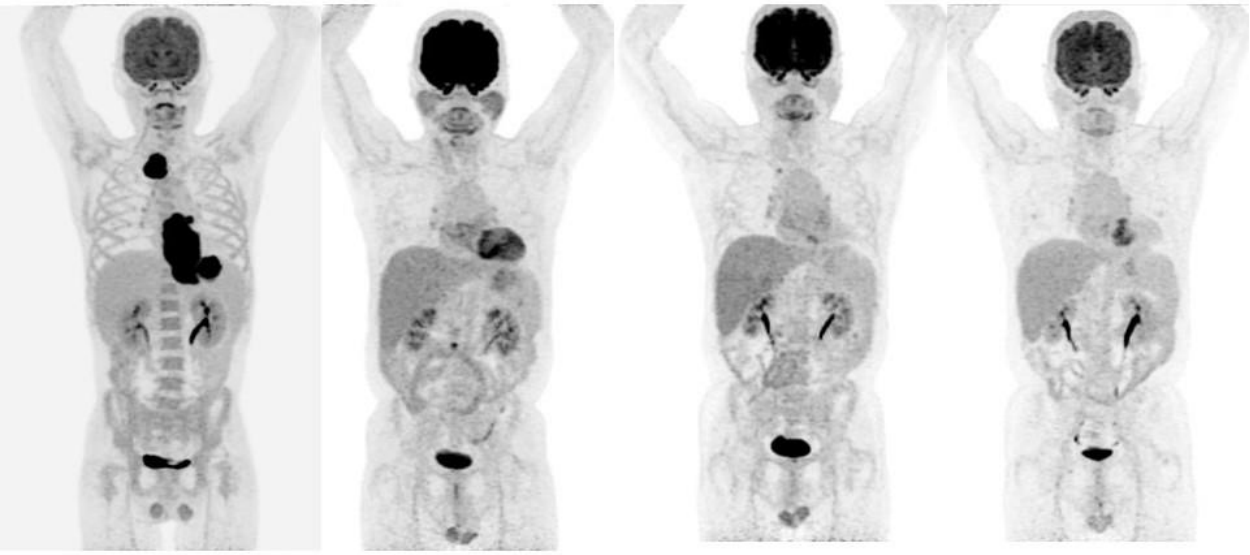
陳*達 Small cell lung cancer



20170509 治療前CT

20171003 治療後CT

葉*宏 Esophageal cancer



20170322治療前
PET-CT

20170913 治療後
PET-CT

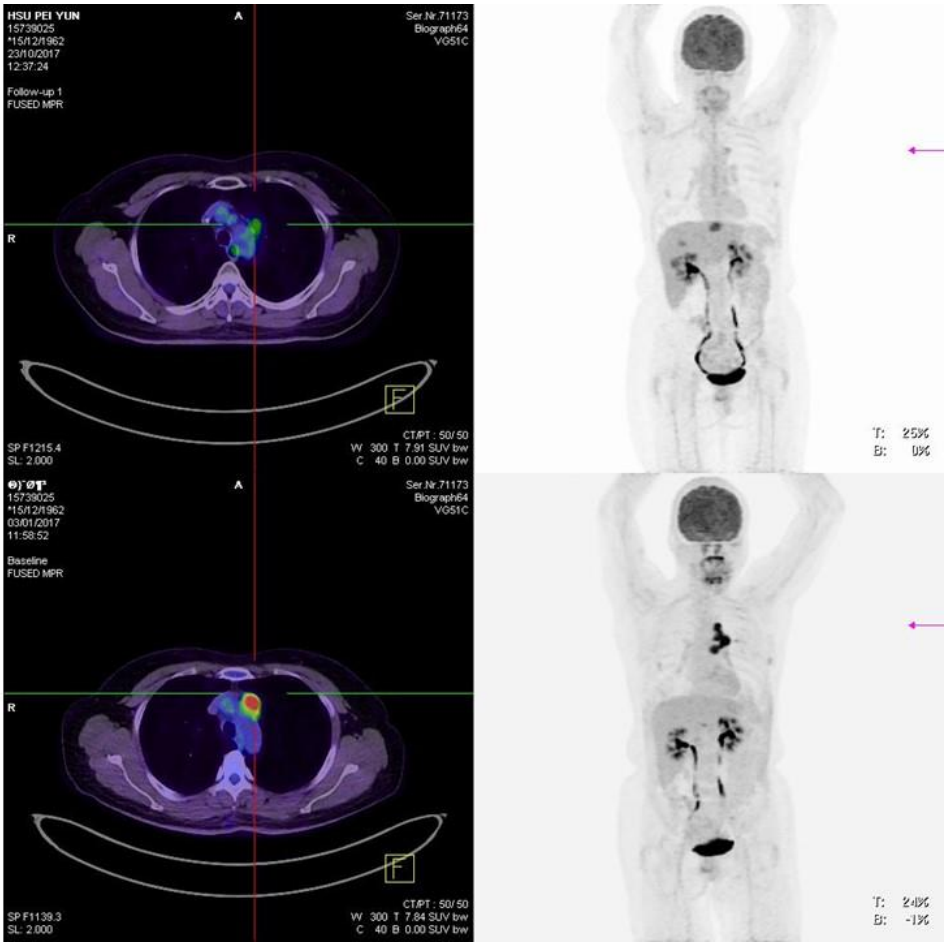
20171229 治療後
持續追蹤PET-CT

20180419 治療後
持續追蹤PET-CT

徐*雲
15739025
Lung

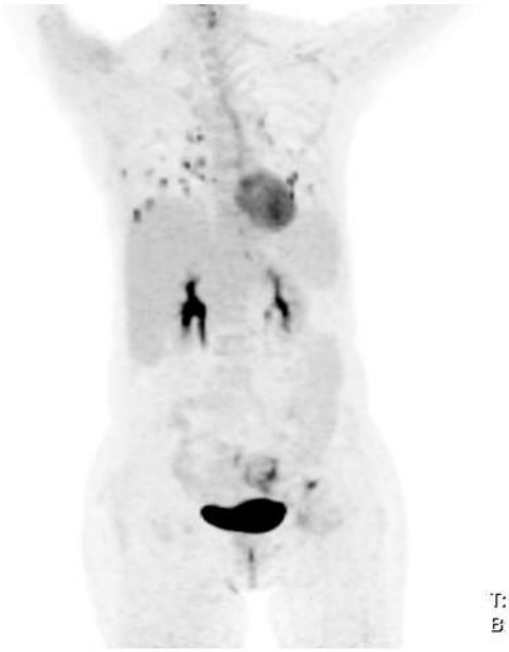
20171026
治療後PET-CT

20170103
治療前PET-CT



余**雲 Cervix cancer lung mets

20170705治療前CT



20170926治療中PET-CT

張*正 Stomach cancer peritoneal seedings

20170323 治療前CT

20170609 治療後CT

Oncothermia as immunotherapy machine ?

- **Will oncothermia change tumor microenvironment ?**
- **Will oncothermia activate immune cells ?**
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- **Will oncothermia increase autoimmune reaction ?**
- **Will oncothermia produce tumor hyperprogression ?**
- **Will oncothermia intensify the effect of immune checkpoint inhibitors ?**

There were 3 patients out of 33 patients developed autoimmune disease, all of them had more than 8 month of treatment-free interval.

Scientifica
Volume 2013, Article ID 857519, 19 pages

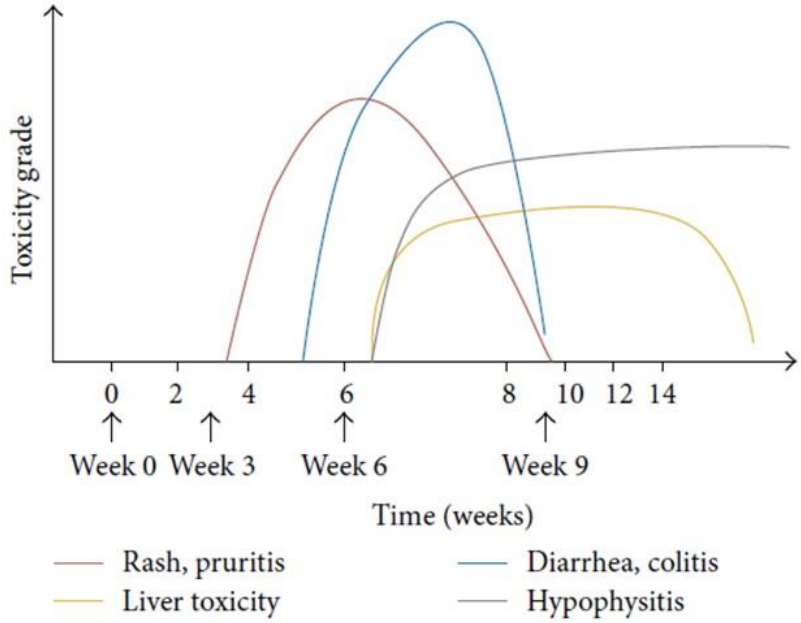
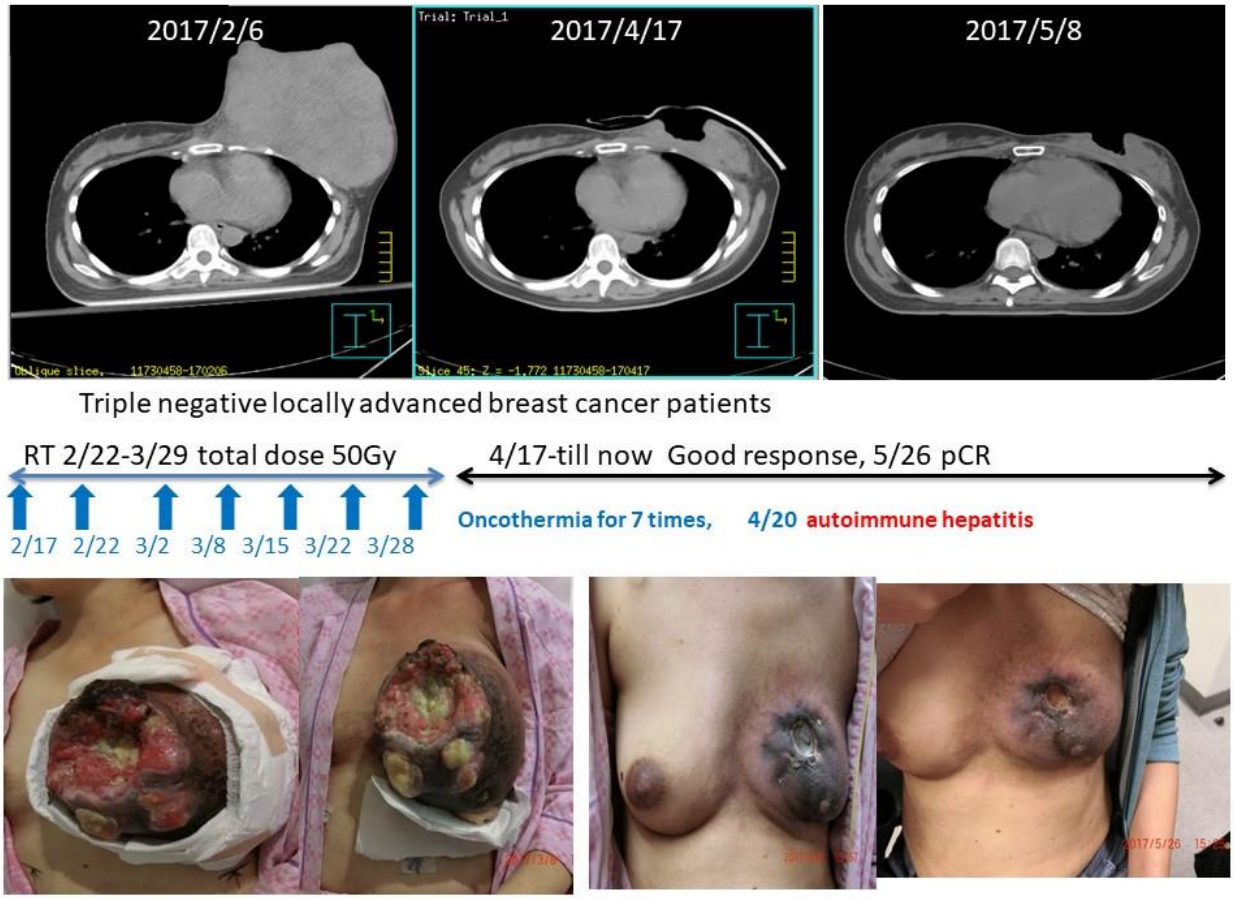
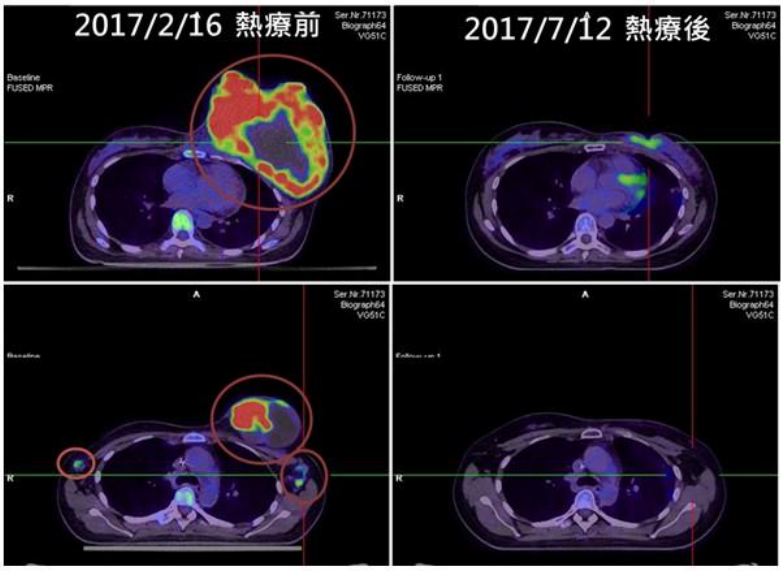


FIGURE 2: Kinetics of appearance of irAEs according to organ system involved [11]; adapted with permission from Weber et al. 2012 [11].





謝*真 11730458

Breast ca with Lung Metastasis

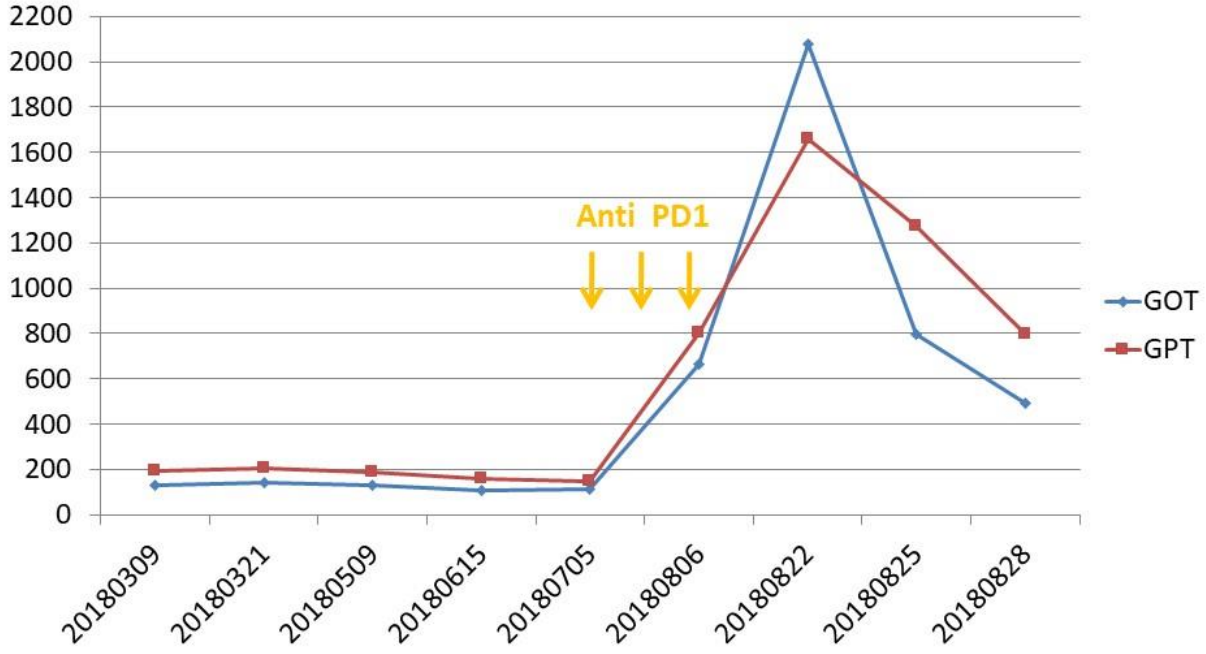
20180328 CT

20180628 CT

20180730 CT

Chi KH et al, Unpublished data

謝*真 11730458



Chi KH et al, Unpublished data

Rt. UCC of renal pelvis with abdomen and liver meta.
RT to abdomen mass 40Gy +OT x 6

20170521治療前CT

20170821治療第一階段完CT

Rt. UCC of renal pelvis with abdomen and liver meta.
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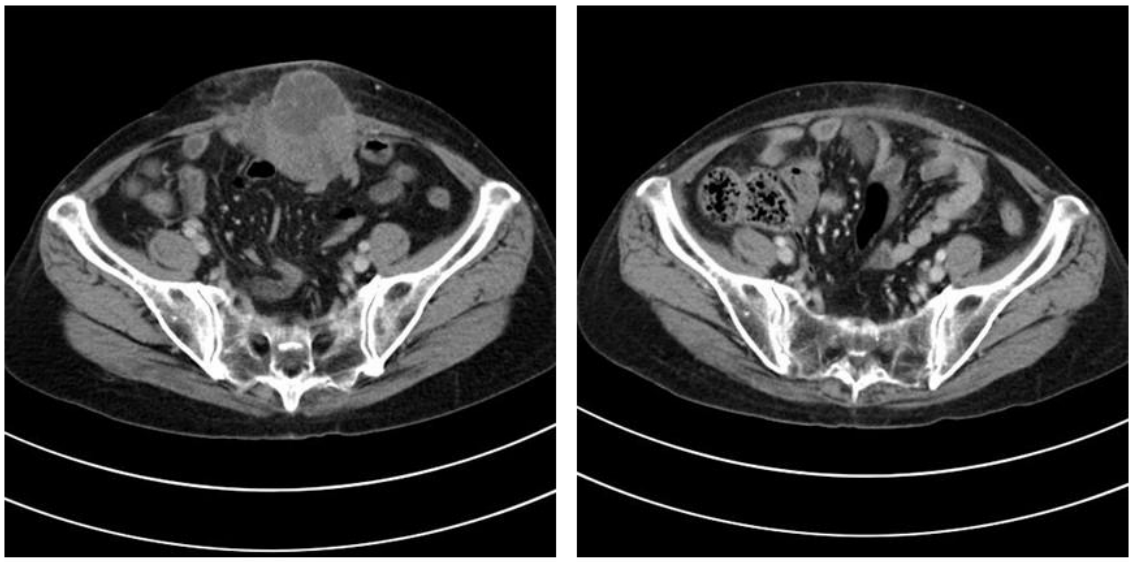
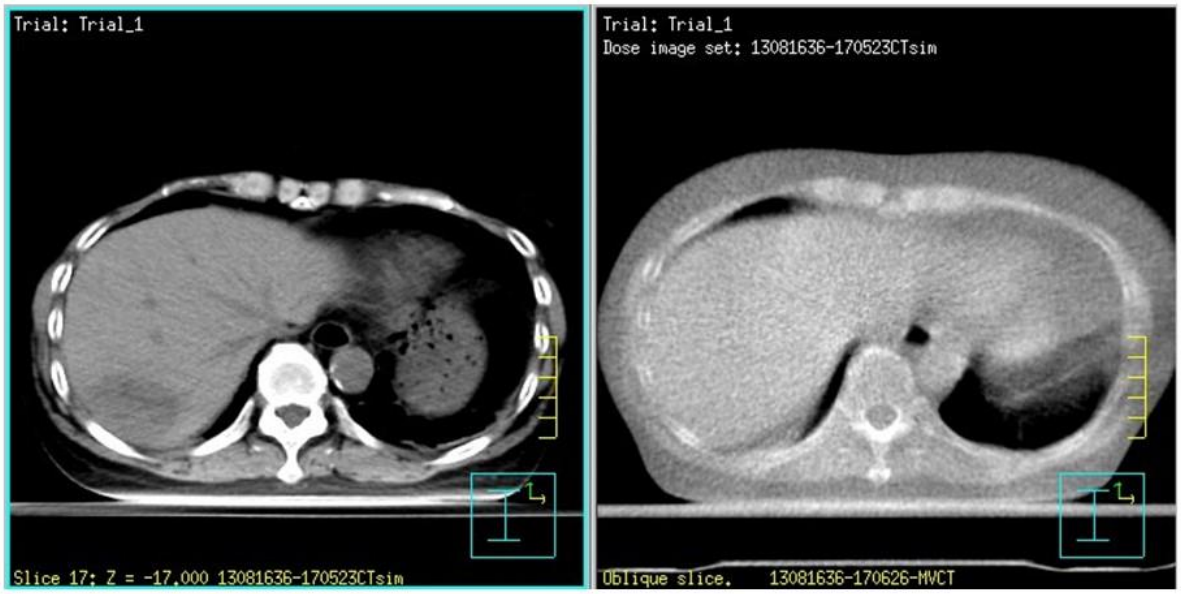


20170521治療前CT　　20170821治療第一階段完CT

Abscopal Effect on Liver mass
(no liver irradiation)



葉*華 130xx636

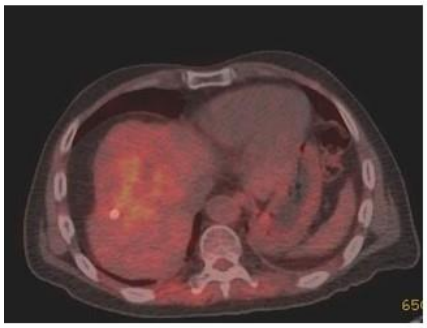
20170521治療前CT

20170821治療完CT

20171120治療後CT

劉*秋 20311631

Cholangiocarcinoma with Liver Metastasis

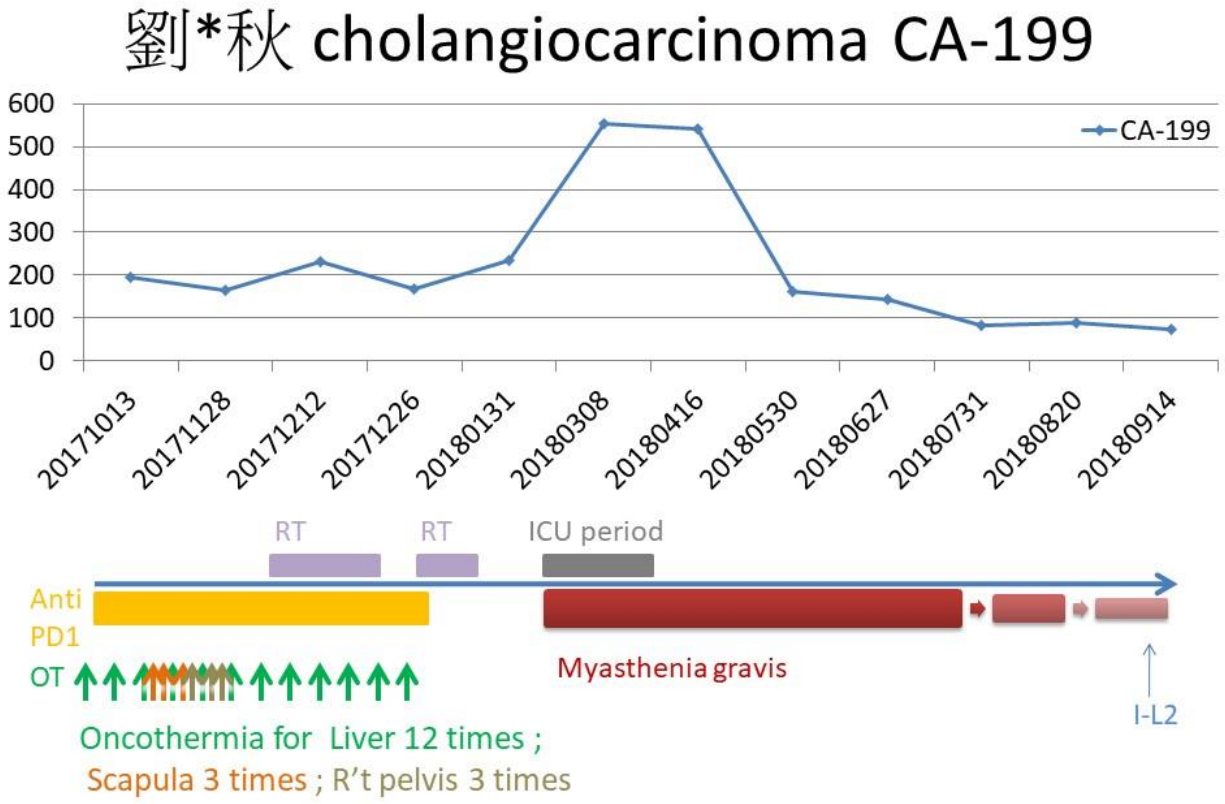


治療前 PET-CT

治療中 CT

治療後 CT

Chi KH et al, Unpublished data



Chi KH et al, Unpublished data

Oncothermia as immunotherapy machine ?

- **Will oncothermia change tumor microenvironment ?**
- **Will oncothermia activate immune cells ?**
- **Will oncothermia increase abscopal effect ?**
- **Will oncothermia increase autoimmune reaction ?**
- **Will oncothermia produce tumor hyperprogression ?**
- **Will oncothermia intensify the effect of immune checkpoint inhibitors ?**

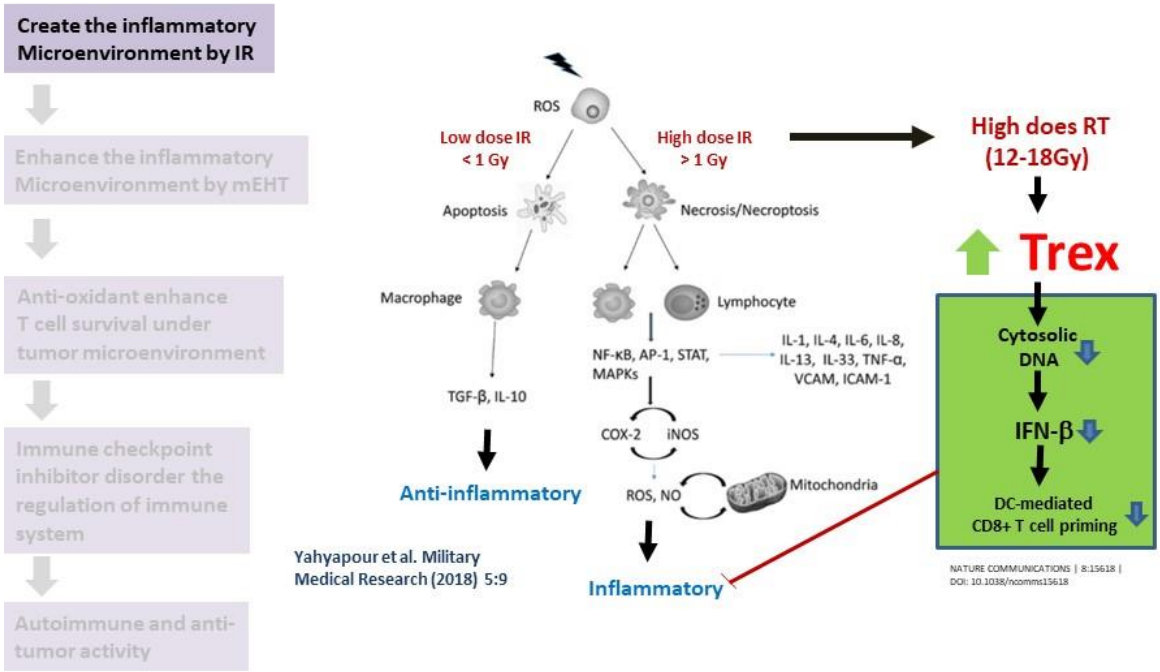
林*珍 Phyllodes tumor

What we have learned ?

- OT must has some radio-sensitization effect.
- Long lasting response only comes with autoimmune reaction. The incidence is 3 out of 33 (9.1%). The incidence of combined GM-CSF +RT is 2/41 (4.9%) if only >90% shrinkage of tumor were counted.
- Large and non-deep seated tumors seemed to have better response by RT + OT.
- Checkpoint inhibitors did not increase the response rates from RT + OT. But severe autoimmune response may be resulted.

How to increase autoimmune response by radiotherapy + oncothermia?

- Anti-CTLA 4 / Anti-PD1 ?
- GM-CSF
- By detecting pathogens to induce autoimmunity ?
- Harness innate immunity cells to adaptive immunity ?
- γδ T cells ?
- Anti-oxidant ?



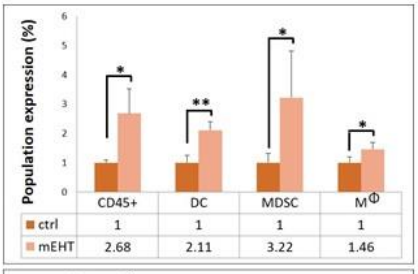
Create the inflammatory Microenvironment by IR

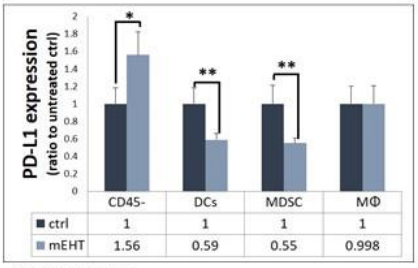
Enhance the inflammatory Microenvironment by mEHT

Anti-oxidant enhance T cell survival under tumor microenvironment

Immune checkpoint inhibitor disorder the regulation of immune system

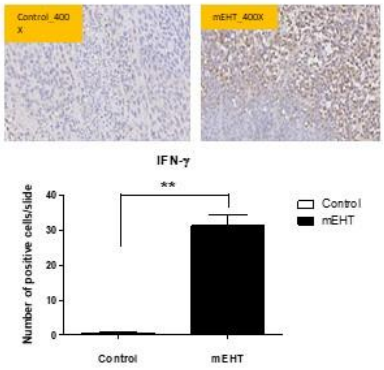
Autoimmune and anti-tumor activity





48h after treatment

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



Wang YS et al, Unpublished data

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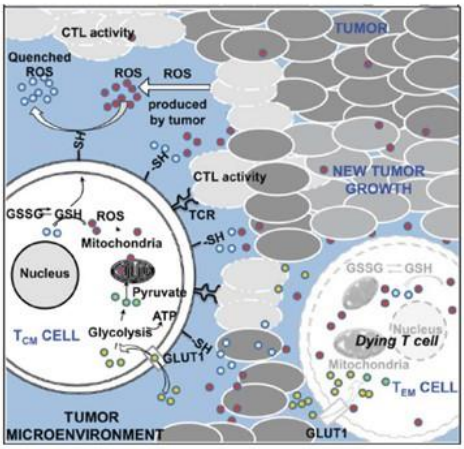
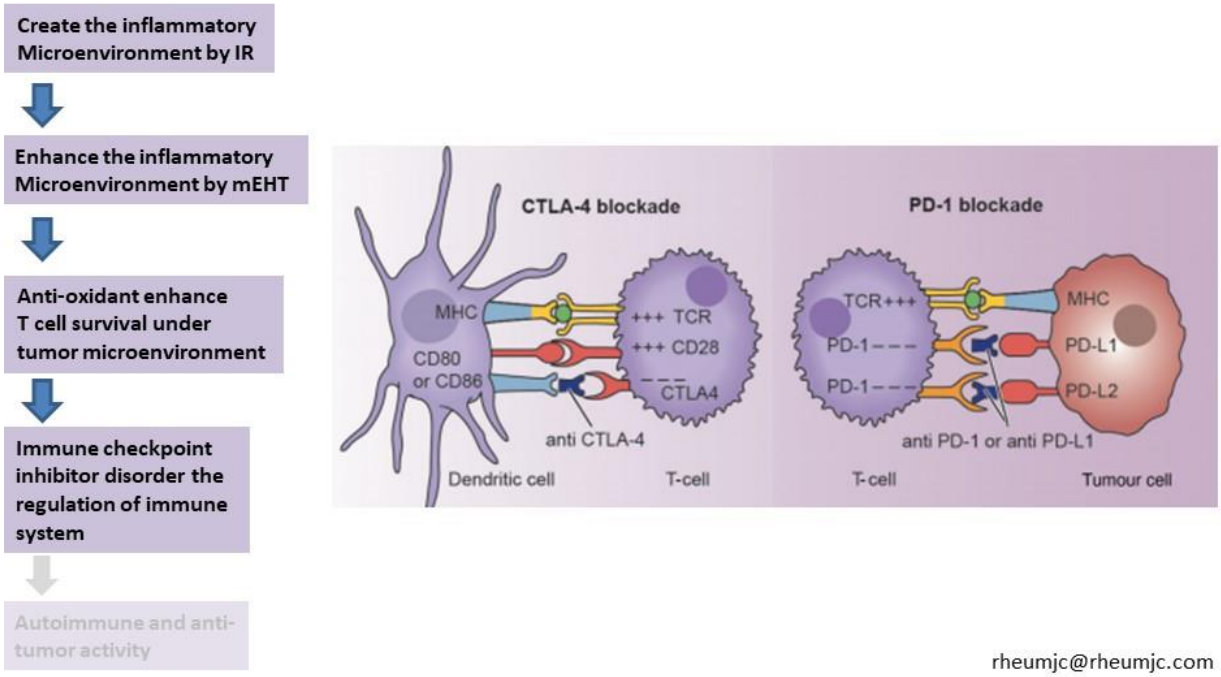


OncoImmunology 4:1, e985942; January 1, 2015;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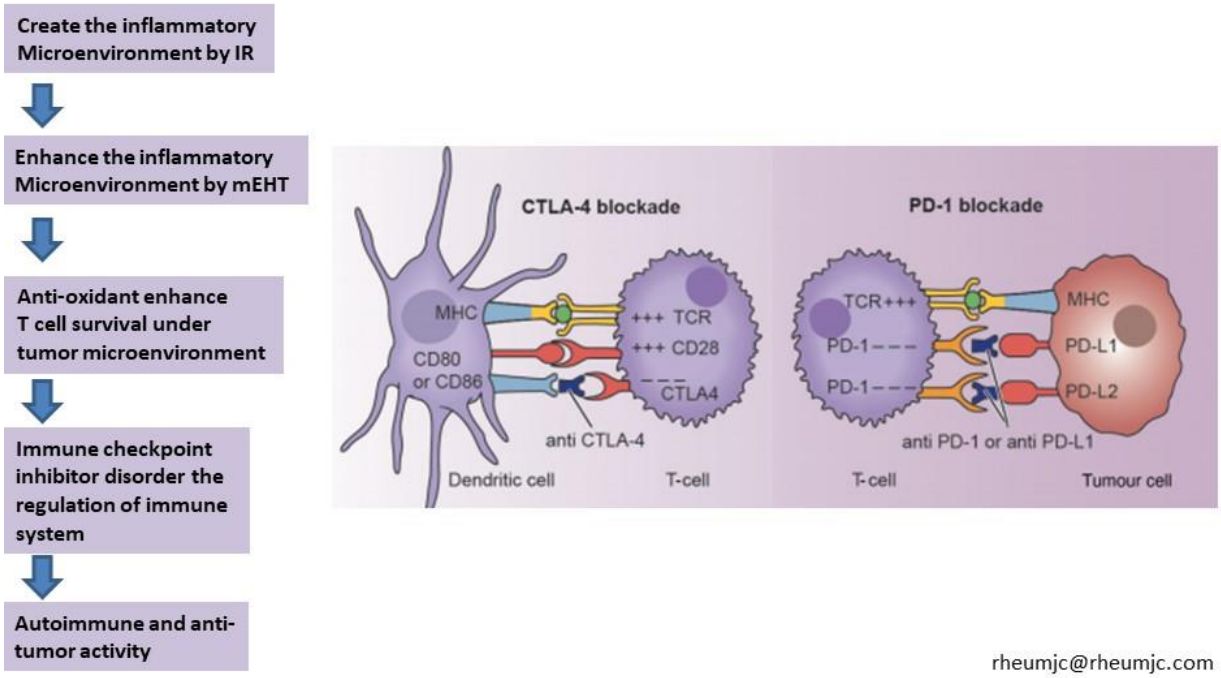
PD-1 blockade
MHC
CD80 or CD86
+++ TCR
+++ CD28
– – –
CTLA4
anti CTLA-4
Dendritic cell
T-cell
TCR+++
PD-1– – –
PD-1– – –
MHC
PD-L1
PD-L2
anti PD-1 or anti PD-L1
T-cell
Tumour cell
rheumjc@rheumjc.com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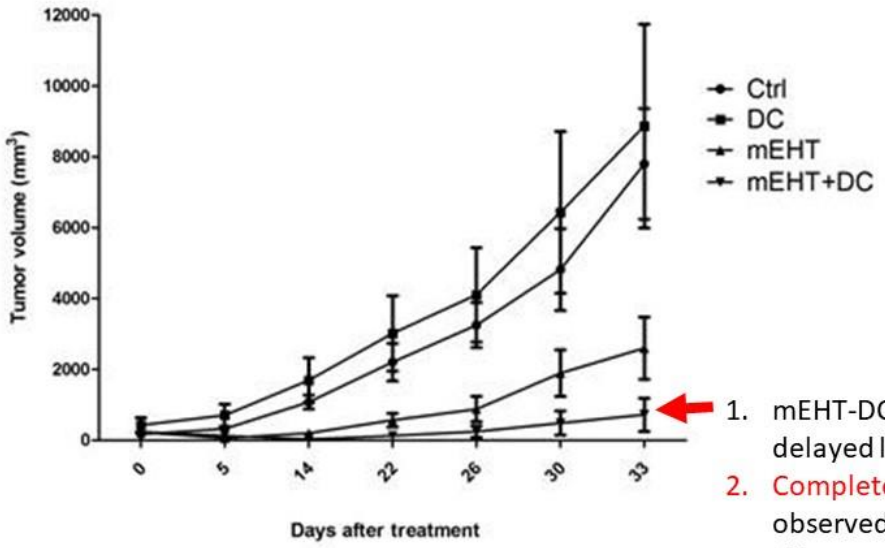
Tumour cell
rheumjc@rheumjc.com

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

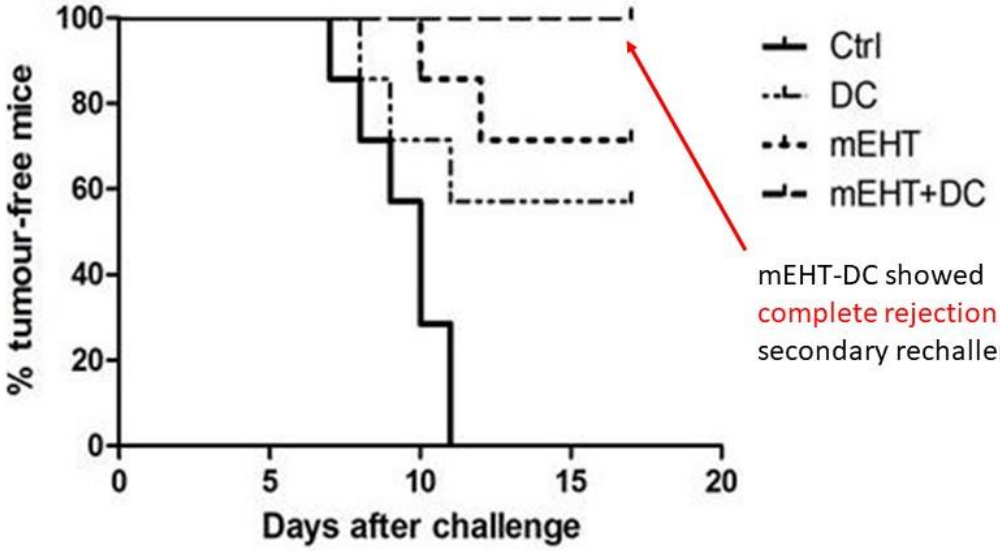


1. mEHT-DC therapy significantly delayed local tumor growth.
2. Complete tumor regression was observed in 5 out of 7 mice in this group.

Tsang et al. BMC Cancer 2015; 15:708

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

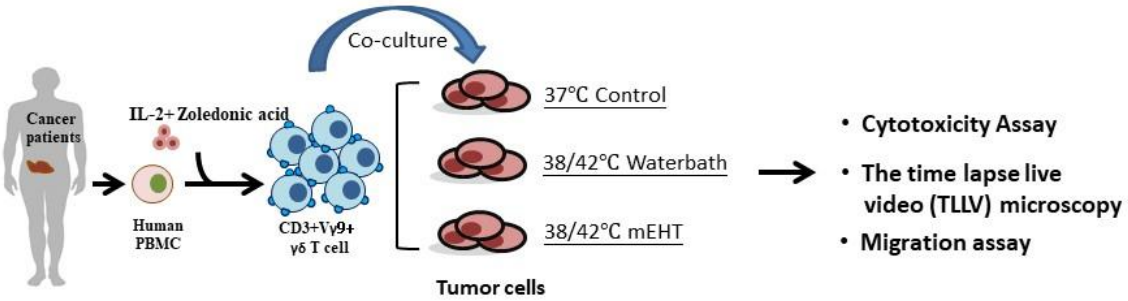
Rechallenge a secondary tumor one month later



mEHT-DC showed complete rejection of a secondary rechallenge

Tsang et al. BMC Cancer 2015; 15:708

To assess the cytotoxicity of γδ T cells on mEHT treated tumor cells



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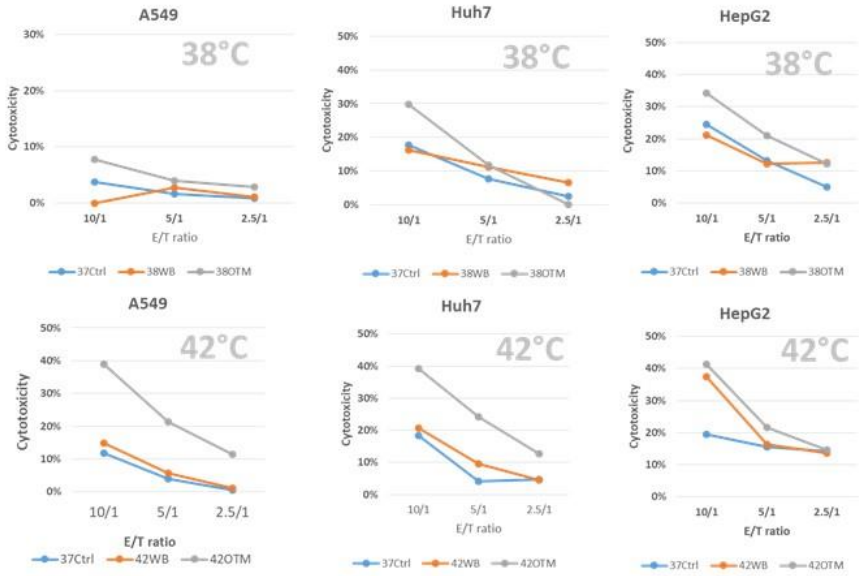
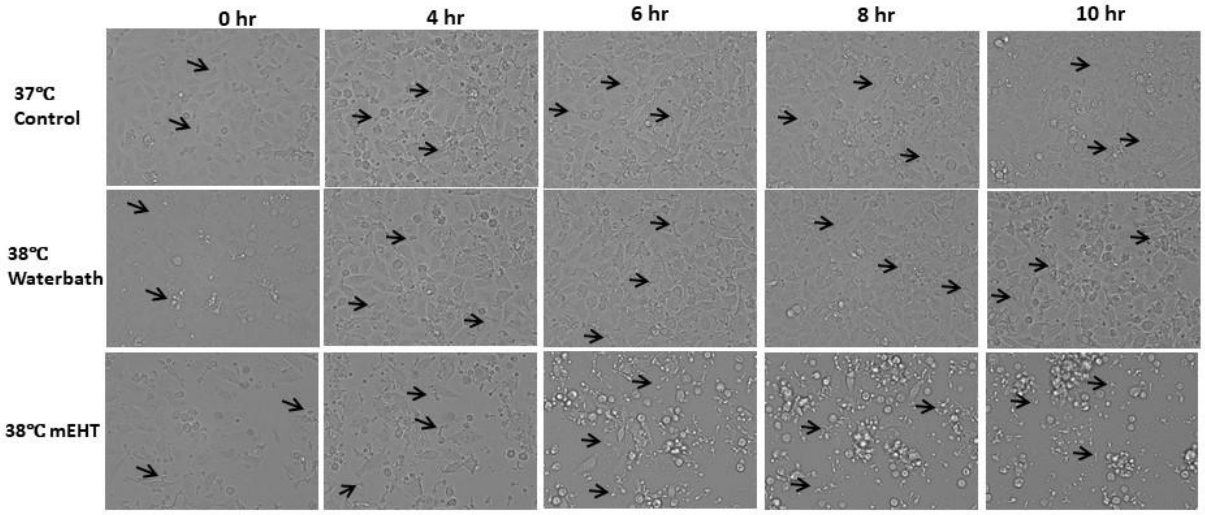
To assess the cytotoxicity of γδT cells on mEHT treated tumor cells



To assess the cytotoxicity of γδT cells on mEHT treated tumor cells

A549 with γδT during 16hr coculture

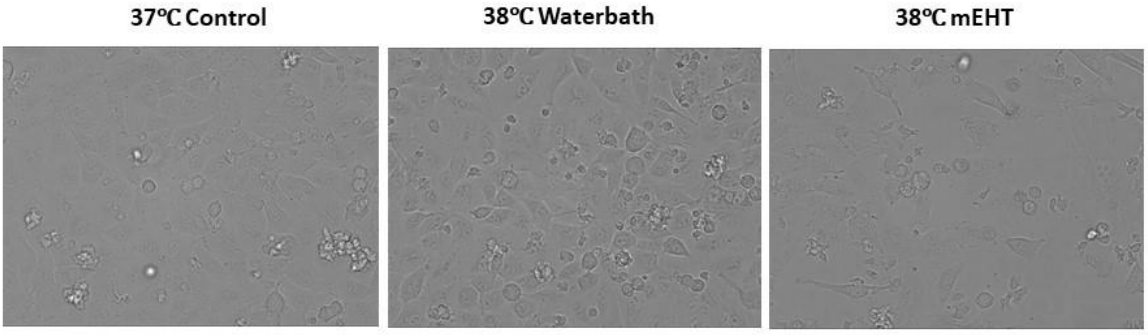


→ γδ T cells

73

To assess the cytotoxicity of γδT cells with or without mEHT treated tumor cells

A549 with γδT during 16hr coculture

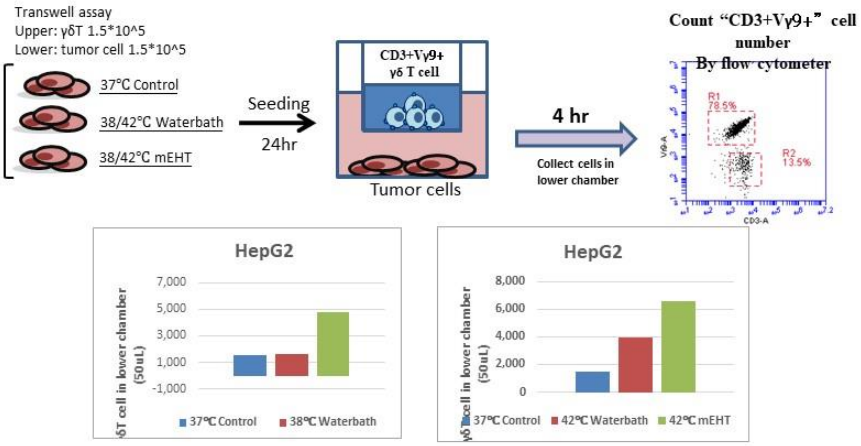


25min/second

- mEHT treatment can enhance γδT cell cytotoxicity

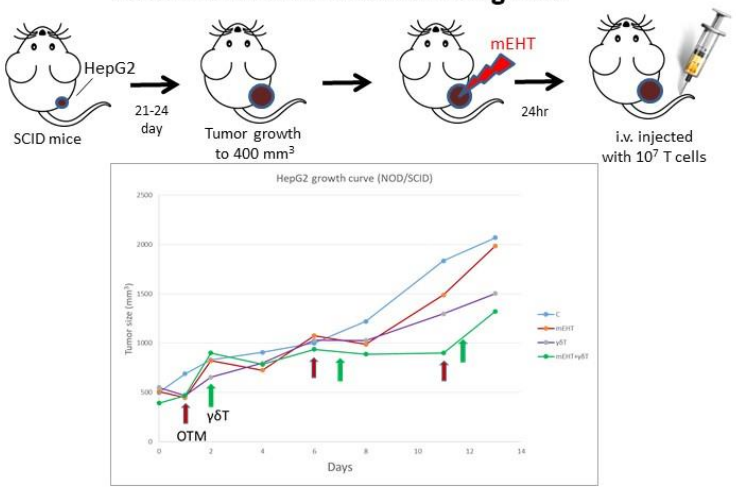
74

To assess the migration ability of γδT cells
After mEHT treatment



• mEHT treatment can enhance γδT cell migration towards tumor cells

To assess the anti-tumor effect of γδT cells on mEHT-treated tumor bearing mice



Thank you for your attention!