Hyperthermia as an immune system activator

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Prof. Dr. Elisabeth Arrojo

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Medical Director
Medical Institute of Advanced Oncology, Madrid, Spain

Citation

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Oncothermia Journal 35, July 2024: 55-99.
https://oncotherm.com/ArrojoE_2024_Hyperthermia-as-an-immune-system-activator_20240601

Philippines, June 1st 2024

Hyperthermia and immune system

Prof. Elisabeth Arrojo Álvarez, MD, PhD

Radiation oncologist

Founder & Medical director of INMOA (Medical Institute of advanced oncology, Madrid and Bilbao, Spain)

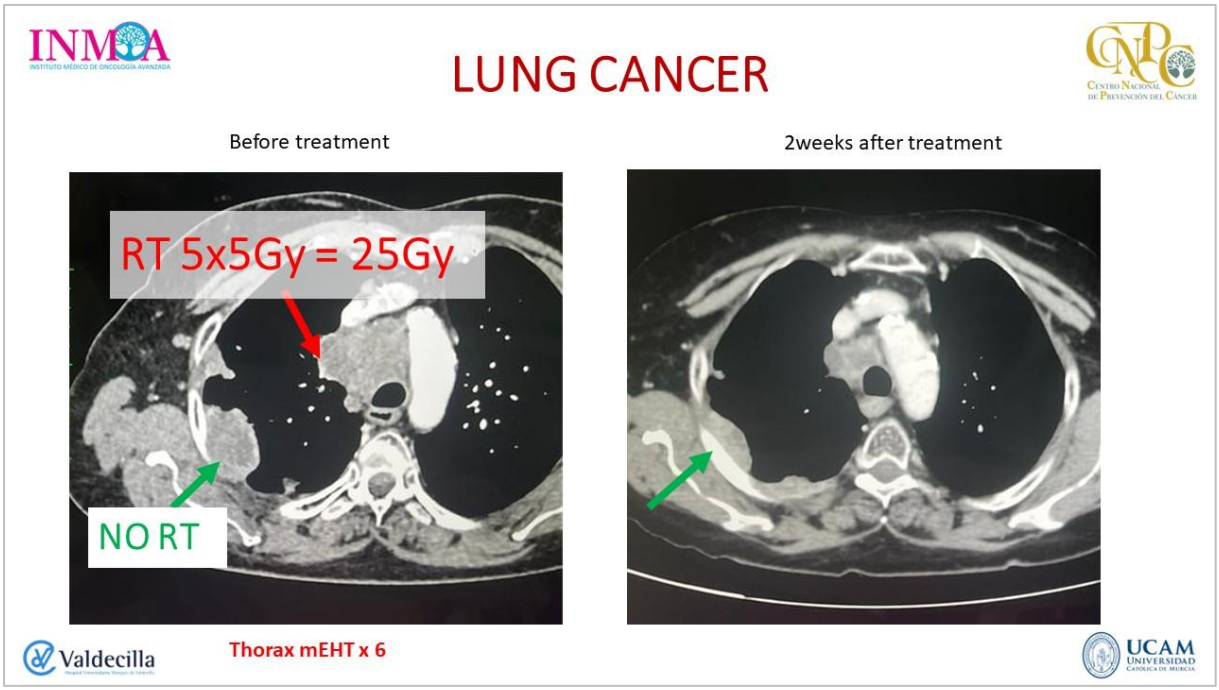
Founder & Director of the National Cancer Prevention Center (Spain)

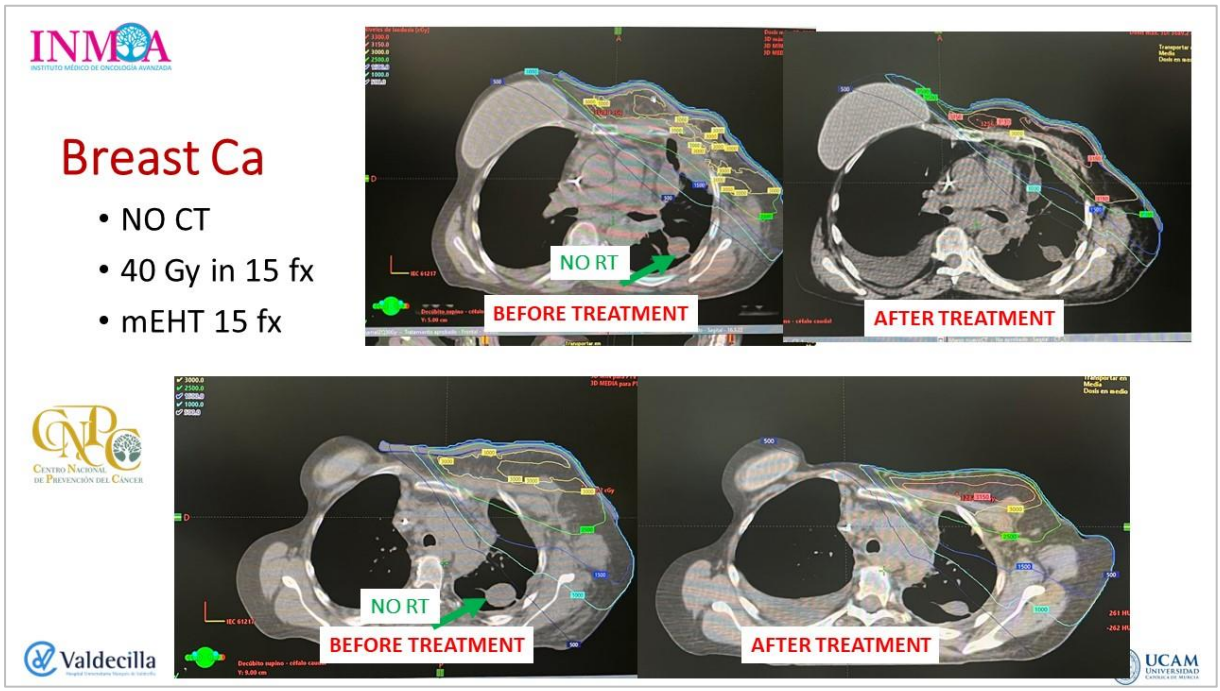
Chair professor in Oncological hyperterhmia at Catholic University of Murcia (UCAM)

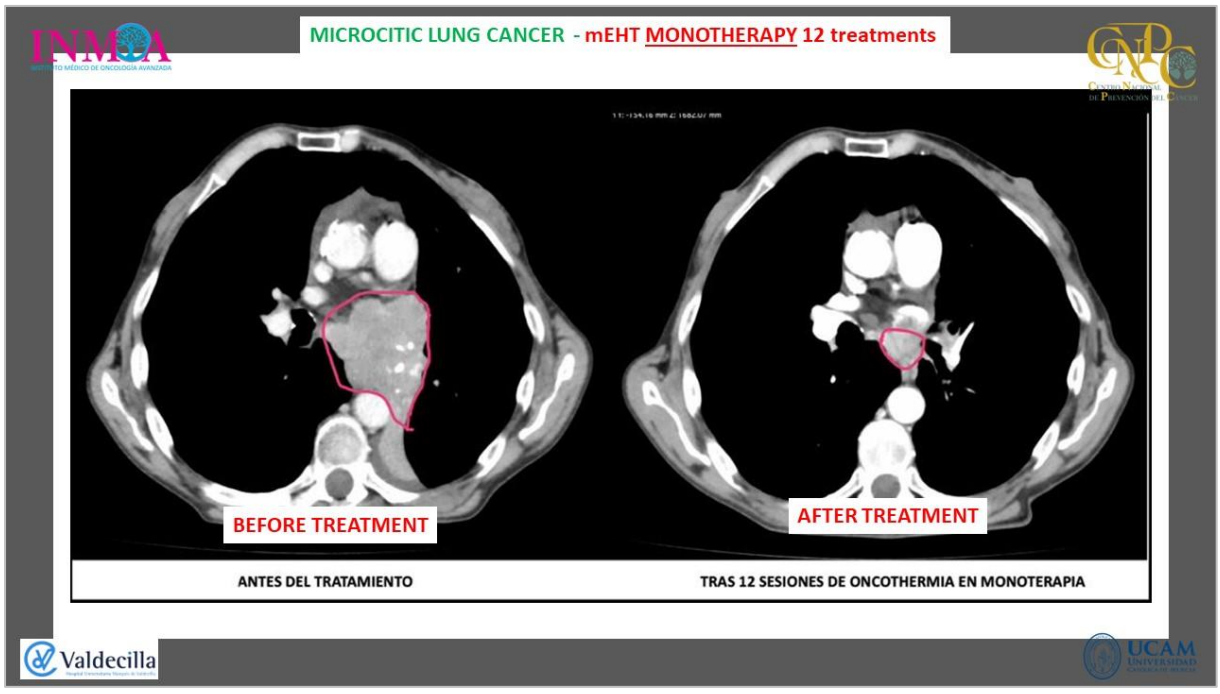
Radiation oncologist at University Hospital Marqués de Valdecilla, Santander, Spain

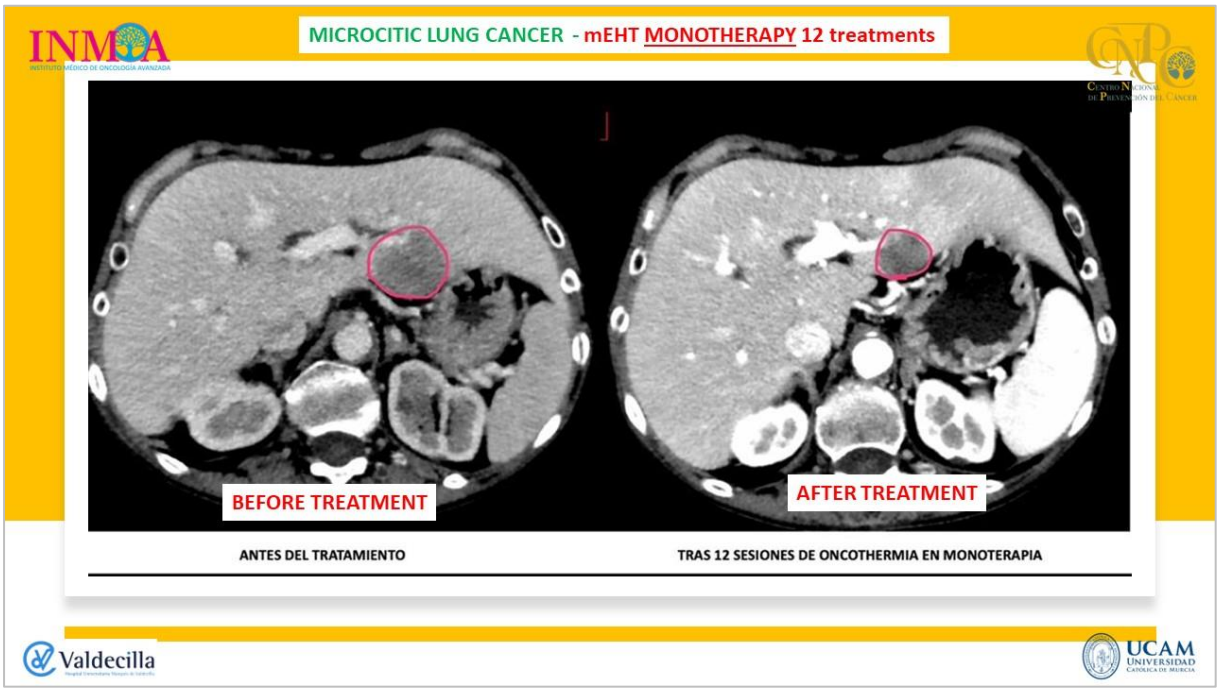
(responsable for the hyperthermia research)

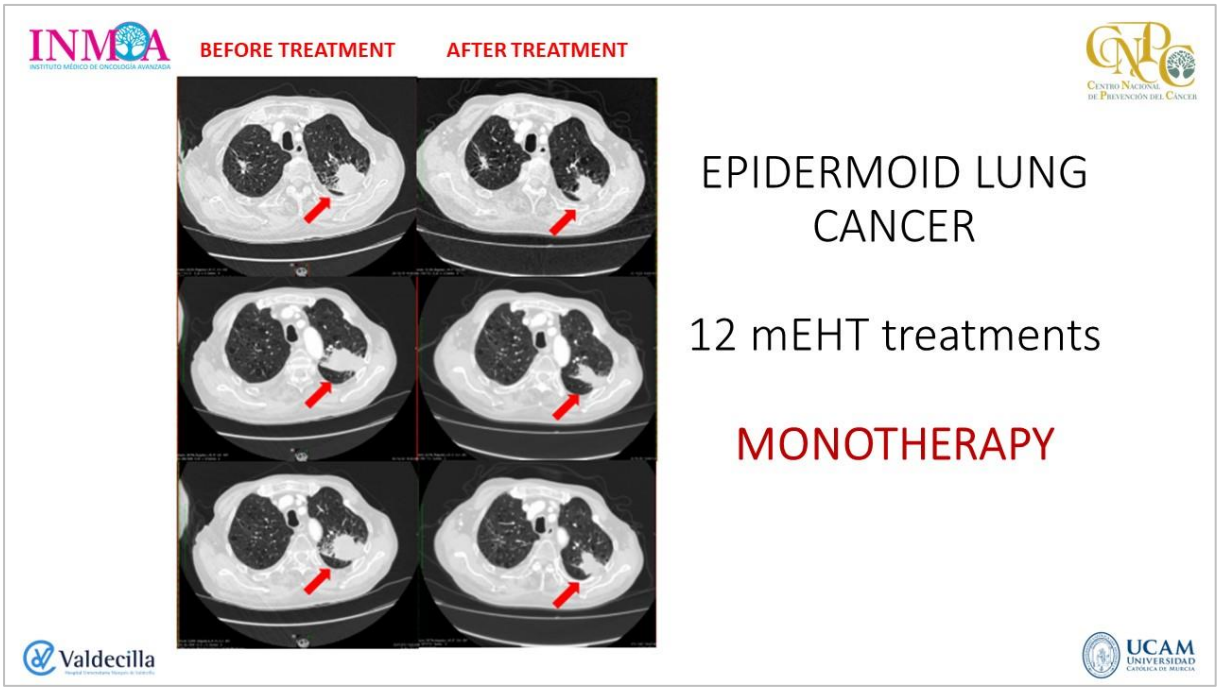

INMOA
Experiences to think about...
Valdecilla
UCAM


INMOA
LUNG CANCER
Before treatment
2weeks after treatment
RT 5x5Gy = 25Gy
NO RT
Thorax mEHT x 6
Valdecilla
UCAM


Breast Ca
• NO CT
• 40 Gy in 15 fx
• mEHT 15 fx
NO RT
BEFORE TREATMENT
AFTER TREATMENT
NO RT
BEFORE TREATMENT
AFTER TREATMENT

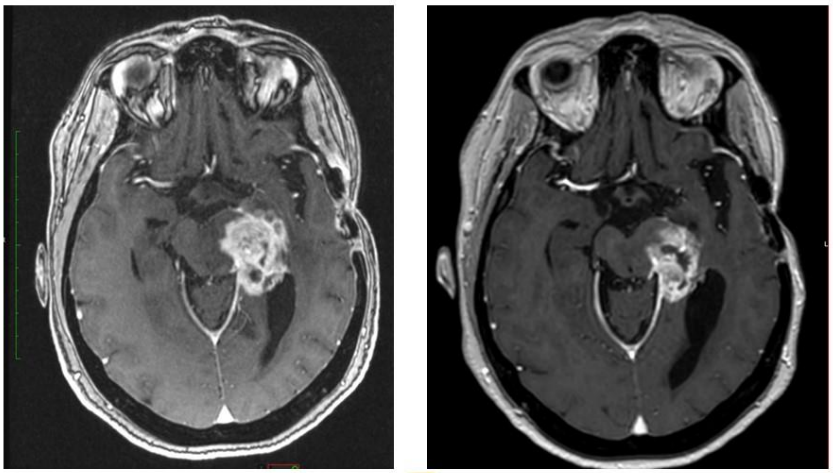

MICROCITIC LUNG CANCER - mEHT MONOTHERAPY 12 treatments
BEFORE TREATMENT
AFTER TREATMENT
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA


MICROCITIC LUNG CANCER - mEHT MONOTHERAPY 12 treatments
BEFORE TREATMENT
AFTER TREATMENT
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA
Valdecilla
UCAM


BEFORE TREATMENT
AFTER TREATMENT
EPIDERMOID LUNG CANCER
12 mEHT treatments
MONOTHERAPY
Valdecilla
UCAM

mEHT MONOTHERAPY

43 yo Female with "IDH –" GBM

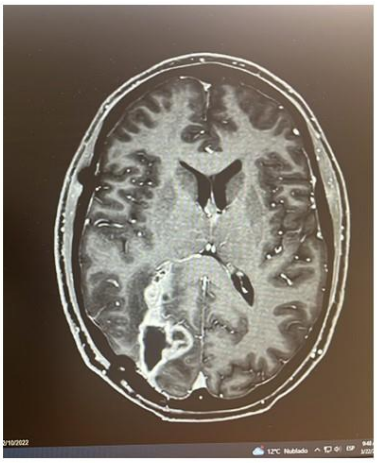


MRI 1 month after mEHT treatment

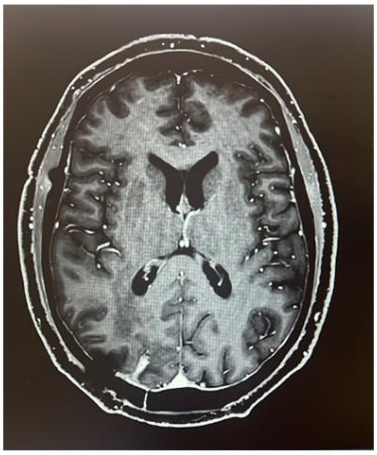
mEHT MONOTHERAPY

52 yo male, GBM IDH negative

Progressed 1 month after standard CT-RT



MRI after progression



MRI after 18 mEHT treatments

frontiers in Oncology

ORIGINAL RESEARCH
published: 24 March 2020
doi: 10.3389/fonc.2020.00376

Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients

*Carrie Anne Minnaar[1], Jeffrey Allan Kotzen[2], Olusegun Akinwale Ayeni[3], Mboyo-Di-Tamba Vangu[3] and Ans Baeyens[1,4]**

[1] Radiobiology, Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2] Radiation Oncology, Wits Donald Gordon Medical Centre, Johannesburg, South Africa, [3] Nuclear Medicine, Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa, [4] Radiobiology, Department of Human Structure and Repair, Ghent University, Ghent, Belgium

OPEN ACCESS

Edited by:
Mary Helen Barcellos-Hoff, University of California, San Francisco, United States

Reviewed by:

Background: A Phase III randomized controlled trial investigating the addition of modulated electro-hyperthermia (mEHT) to chemoradiotherapy for locally advanced cervical cancer patients is being conducted in South Africa (Human Research Ethics Committee approval: M1704133; ClincialTrials.gov ID: NCT03332069). Two hundred and ten participants were randomized and 202 participants were eligible for six month local disease control evaluation. Screening ^{18}F-FDG PET/CT scans were conducted and

randomised controlled Phase III trial involving 210 participants evaluating chemoradiotherapy (CRT)

- **Abscopal effect**: **systemic response to RT** in which **non-irradiated lesions respond after irradiation of the primary** treatment site.
  - Immune system activation by radiotherapy.
  - Very low frequency.

Cervical Cancer - Phase III trial

- **Results:**
  - **Abscopal response mEHT group 24.1%** (13 of 54) **vs 5.6%** (3 of 54) control group (p=0.013).
  - No significant difference between VIH + and -.
  - Multivariant analysis not significant:
    - Age
    - Cispatin
    - Days to PET-CT
    - Total RT

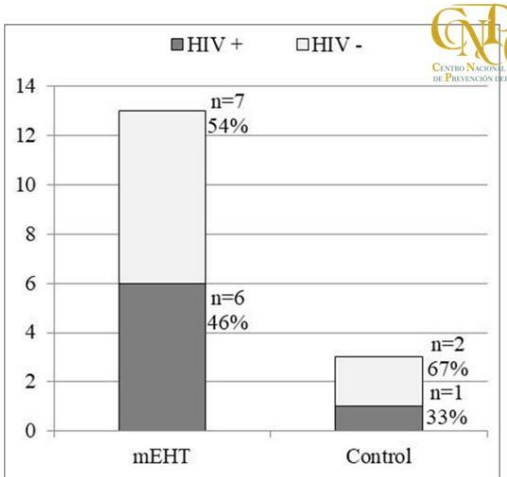
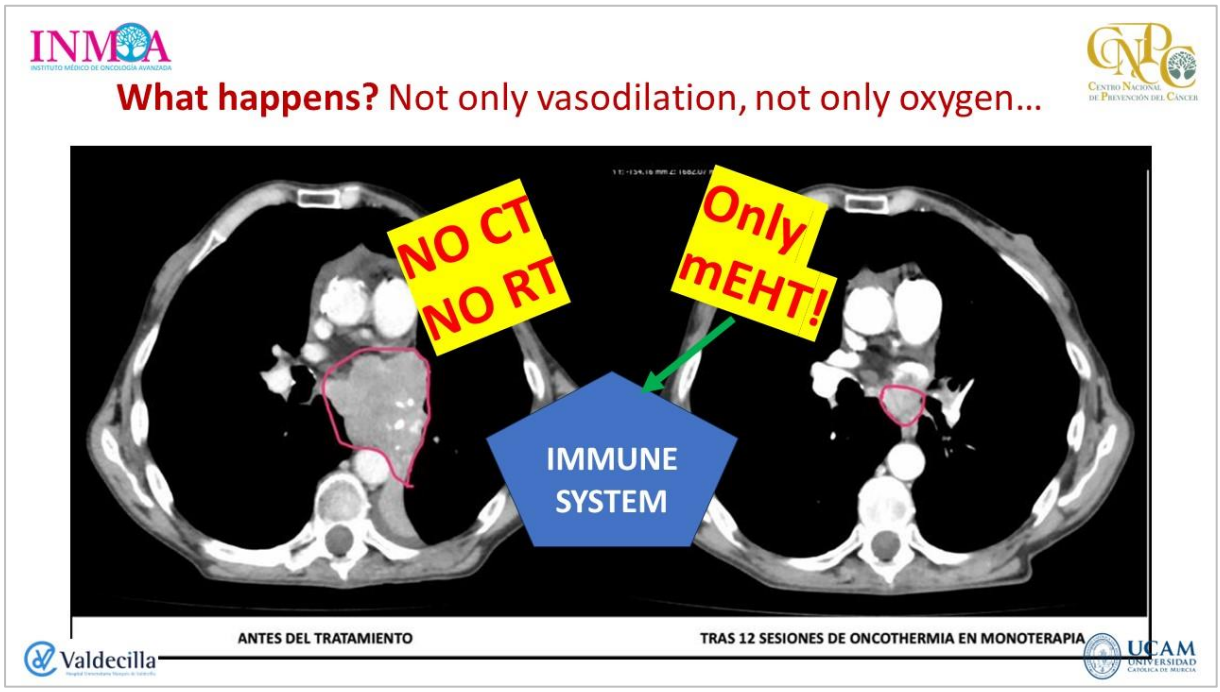
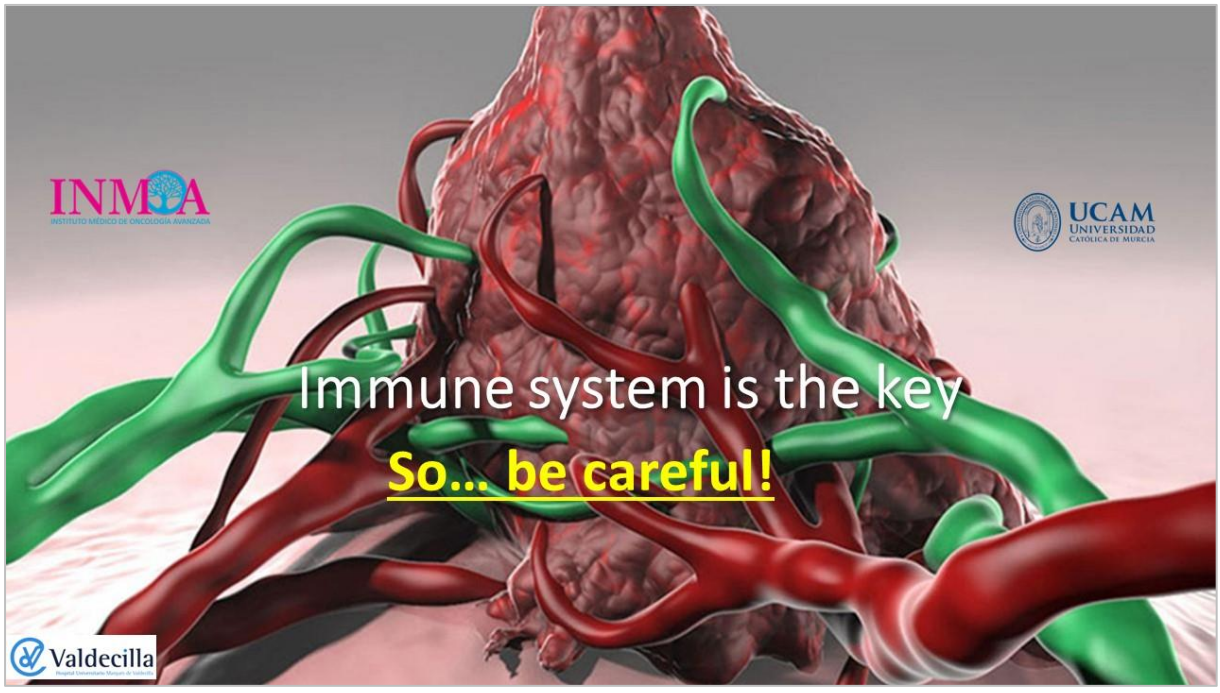
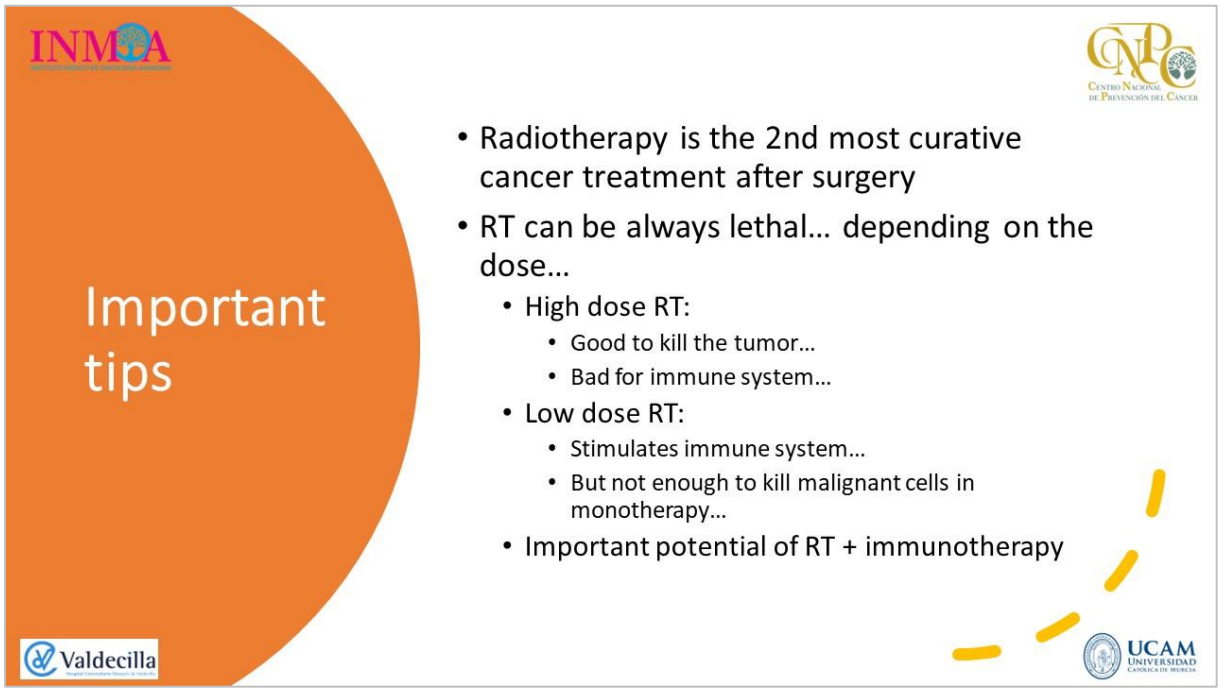
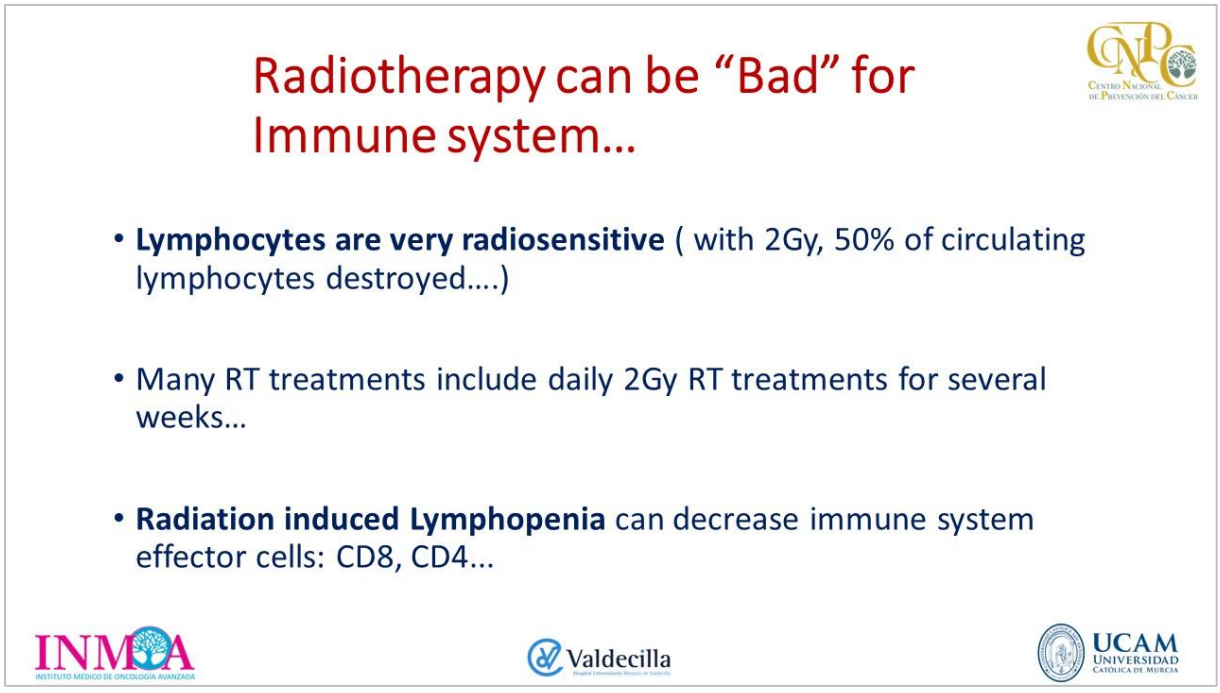


FIGURE 2 | Frequency of observed abscopal effect in HIV-positive and HIV-negative participants in each treatment group. A significant difference between the frequency of abscopal effect was noted between the mEHT Group (13 out of 54[24.1%]) and the Control Group (3 out of 54 [5.6%]) (p = 0.013). There was no significant difference in frequency of the observed abscopal between the HIV-positive and HIV-negative participants. mEHT, Modulated Electro-Hyperthermia; HIV, Human Immunodeficiency Virus.

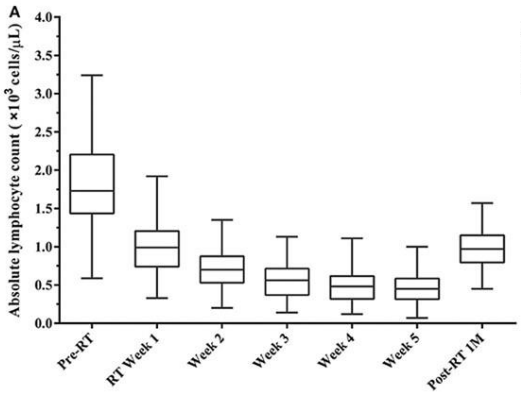

What happens? Not only vasodilation, not only oxygen…
NO CT
NO RT
Only
mEHT!
IMMUNE
SYSTEM
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA


Immune system is the key
So… be careful!


INMOA
Important tips
• Radiotherapy is the 2nd most curative cancer treatment after surgery
• RT can be always lethal… depending on the dose…
• High dose RT:
• Good to kill the tumor…
• Bad for immune system…
• Low dose RT:
• Stimulates immune system…
• But not enough to kill malignant cells in monotherapy…
• Important potential of RT + immunotherapy
Valdecilla
UCAM

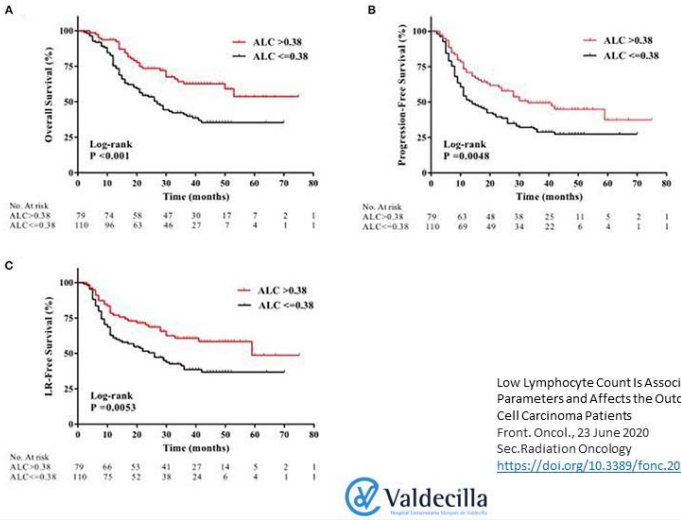

Radiotherapy can be "Bad" for Immune system…
• **Lymphocytes are very radiosensitive** (with 2Gy, 50% of circulating lymphocytes destroyed….)
• Many RT treatments include daily 2Gy RT treatments for several weeks…
• **Radiation induced Lymphopenia** can decrease immune system effector cells: CD8, CD4…
INMOA
Valdecilla
UCAM

Long treatments… (2Gy/fx)



Low Lymphocyte Count Is Associated With Radiotherapy Parameters and Affects the Outcomes of Esophageal Squamous Cell Carcinoma Patients
Front. Oncol., 23 June 2020
Sec.Radiation Oncology

Destroying lymphocytes negatively impacts survival…



Low Lymphocyte Count Is Associated With Radiotherapy Parameters and Affects the Outcomes of Esophageal Squamous Cell Carcinoma Patients
Front. Oncol., 23 June 2020
Sec.Radiation Oncology
https://doi.org/10.3389/fonc.2020.00997

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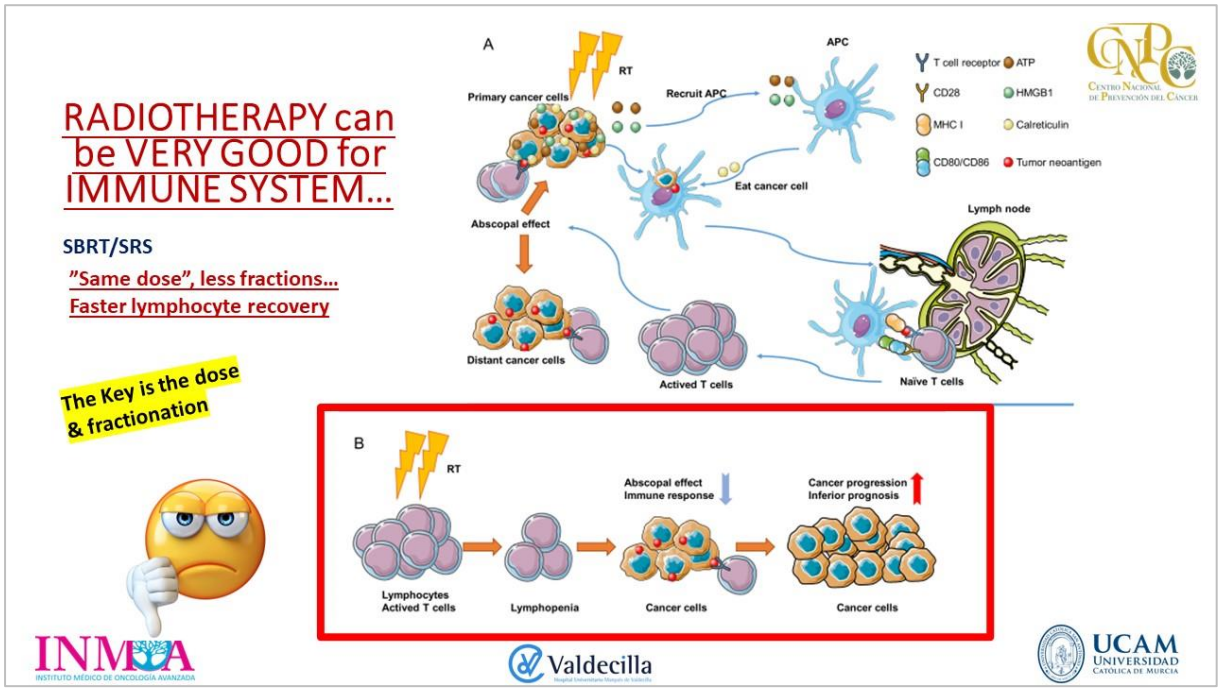

RADIOTHERAPY can be VERY GOOD for IMMUNE SYSTEM...
SBRT/SRS
"Same dose", less fractions...
Faster lymphocyte recovery
The Key is the dose & fractionation
A
RT
Primary cancer cells
Recruit APC
APC
Eat cancer cell
Abscopal effect
Distant cancer cells
Actived T cells
Lymph node
Naive T cells
T cell receptor
ATP
CD28
HMGB1
MHC I
Calreticulin
CD80/CD86
Tumor neoantigen
B
RT
Abscopal effect
Immune response
Cancer progression
Inferior prognosis
Lymphocytes
Actived T cells
Lymphopenia
Cancer cells
Cancer cells
INMOA
Valdecilla
UCAM
UNIVERSIDAD CATÓLICA DE MURCIA


INMOA
High and low dose RT combination?
Let's try!
Valdecilla
UCAM

Radiotherapy and Oncology 162 (2021) 60–67

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial

Roshal R. Patel [a,i,1], Kewen He [a,j,1], Hampartsoum B. Barsoumian [a], Joe Y. Chang [a], Chad Tang [a], Vivek Verma [a], Nathan Comeaux [a], Stephen G. Chun [a], Saumil Gandhi [a], Mylene T. Truong [b], Jeremy J. Erasmus [b], David S. Hong [e], Percy P. Lee [a], Matthew S. Ning [a], Quynh-Nhu Nguyen [a], John V. Heymach [d], Mehmet Altan [d], George Blumenschein [d], Frank V. Fossella [d], Duygu Sezen [a,k], Dawei Chen [a,i], Brett W. Carter [b], Michael A. Davies [c], Isabella C. Glitza [d], Adi Diab [c], Renata Ferrarotto [d], Maria E. Cabanillas [f], Ying Yuan [g], Shalin J. Shah [a], Edwin R. Parra [h], Baohua Sun [h], Maria Angelica Cortez [a], James W. Welsh [a,*]

[a] Departments of Radiation Oncology, The University of Texas MD Anderson Cancer Center; [b] Departments of Thoracic Imaging, The University of Texas MD Anderson Cancer Center; [c] Departments of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center; [d] Departments of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center; [e] Departments of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center; [f] Departments of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center; [g] Biostatistics, The University of Texas MD Anderson Cancer Center; [h] Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston; [i] Albany Medical College, Albany, USA; [j] Departments of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China; [k] Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial.

- Pathological confirmed M1, at least one metastatic lesion amenable to RT and progression of disease on immunotherapy.
- 74 patients (NSCLC, n = 38; melanoma n = 21)
  - **39 received HD-RT (20–70 Gy total; 3–12.5 Gy/f)**
  - **35 received HD-RT + LD-RT (0.5–2 Gy/f up to 1–10 Gy total)**
  - **Went on with same immunotherapy they had progressed to.**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **Patients received IT for a median of 7.1 months before RT.**
- **No significant differences in patients' characteristics between groups.**
- **88% of the evaluable patients received at least 1 cycle of immunotherapy after RT** (29/34 in the HD-RT + LD-RT and 34/38 in the HD-RT cohort).
- **Of patients continuing to immunotherapy after RT, most patients 95%, continued on the same regimen and 54% continued to receive the same agent at 4 months.**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

Table 1
Clinical response by treatment group.

	High + Low Dose No. (%)	High-Dose-Only No. (%)	
CR	2 (6%)	1 (3%)	
PR	7 (21%)	4 (10%)	
SD	14 (41%)	16 (42%)	
PD	11 (32%)	17 (45%)	
			P value
DCR[a]	16 (47%)	14 (37%)	0.38
ORR[b]	9 (26%)	5 (13%)	0.27

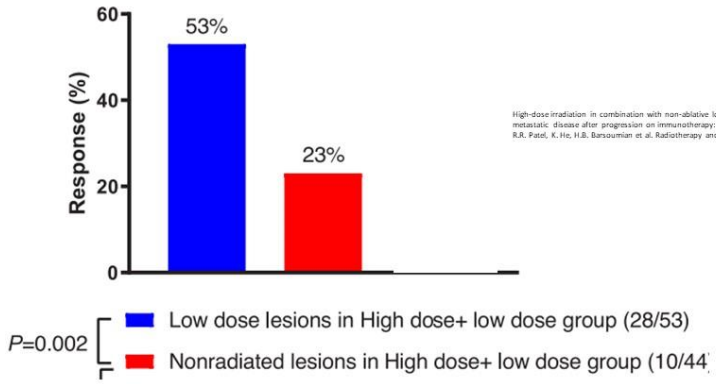
[a]Disease control rate: CR/PR/SD at 4 months.
[b]Overall response rate: CR/PR at any time.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **HDRT + LD-RT**

HD-RT: high-dose radiotherapy;
LD-RT: low-dose radiotherapy.

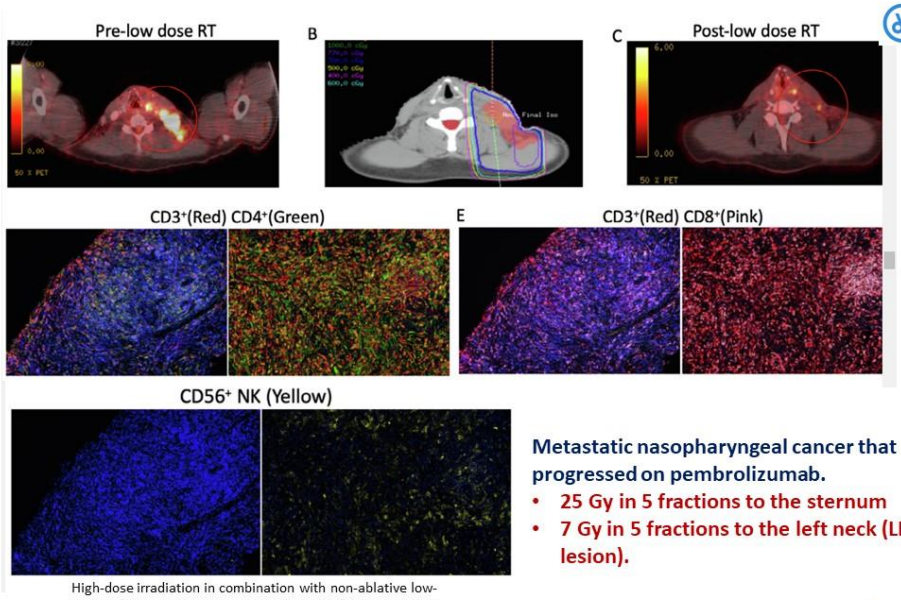


High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **Patients with PD after more than 6 months of immunotherapy were more likely to achieve an objective response** (CR/PR, i.e., met the primary endpoint) **in both** the overall cohort (54% vs. 26%, **P = 0.02**) and the high-/low-dose RT cohort alone (69% versus 30%, **P = 0.03**).

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67



Metastatic nasopharyngeal cancer that progressed on pembrolizumab.

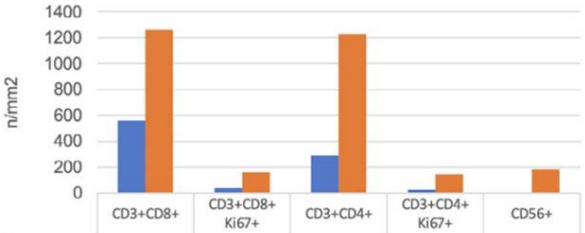
- **25 Gy in 5 fractions to the sternum**
- **7 Gy in 5 fractions to the left neck (LD-RT lesion).**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **LD-RT induced a remarkable increase in immune cell infiltration into the irradiated lesions:**
  - **300% increase in CD4+ T cells**
  - **187% increase and NK cells.**

G

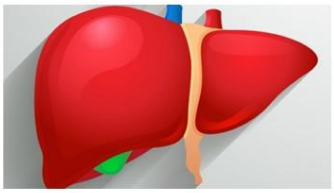


	CD3+CD8+	CD3+CD8+ Ki67+	CD3+CD4+	CD3+CD4+ Ki67+	CD56+
pre L-XRT	558.02	41.35	287.81	26.20	0.00
post L-XRT	1261.51	158.77	1233.01	144.51	187.60
% change	126 %	284%	300%	452%	-

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

- **HD-RT starts movement: Activates Ag release and presentation.**
- **LD-RT: "modulates" and power response.**

- **Liver, an "special " organ…**



frontiers in Immunology

MINI REVIEW
published: 15 December 2021
doi: 10.3389/fimmu.2021.812210

Novel Use of Low-Dose Radiotherapy to Modulate the Tumor Microenvironment of Liver Metastases

*Kewen He[1,2,3], Hampartsoum B. Barsoumian[3], Genevieve Bertolet[3], Vivek Verma[4], Carola Leuschner[3], Eugene J. Koay[5], Ethan B. Ludmir[6], Ethan Hsu[3], Esha Pisipati[3], Tiffany A. Voss[3], Nahum Puebla-Osorio[3], María Angelica Cortez[3] and James W. Welsh[3]**

[1] Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [2] Cheeloo College of Medicine, Shandong University, Jinan, China, [3] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [4] Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, United States, [5] Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [6] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

OPEN ACCESS

Edited by:
Anil Shanker,
Meharry Medical College,

Despite multiple therapeutic approaches, the presence of liver metastases carries a guarded prognosis, urgently necessitating further clinical and scientific research to develop curative interventions. The liver is an immunoprivileged organ that suppresses

- Although immunotherapies have shown significant clinical benefit in patients with extrahepatic tumors, **patients with metastases to the liver had been historically identified to respond poorly to immunotherapy.**

ESMO

Annals of Oncology 29: 959–965, 2018
doi:10.1093/annonc/mdy041
Published online 21 February 2018

ORIGINAL ARTICLE

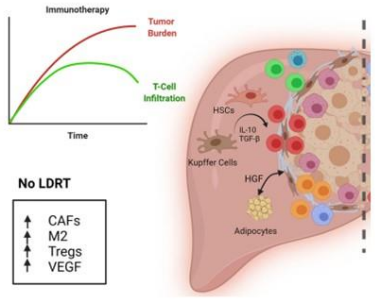
Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases

E. E. Vokes[1*], N. Ready[2], E. Felip[3], L. Horn[4], M. A. Burgio[5], S. J. Antonia[6], O. Arén Frontera[7], S. Gettinger[8], E. Holgado[9], D. Spigel[10,11], D. Waterhouse[12,13], M. Domine[14], M. Garassino[15], L. Q. M. Chow[16], G. Blumenschein Jr[17], F. Barlesi[18], B. Coudert[19], J. Gainor[20], O. Arrieta[21], J. Brahmer[22], C. Butts[23], M. Steins[24], W. J. Geese[25], A. Li[25], D. Healey[25] & L. Crinò[5]

For example, a subanalysis of two phase-III trials, demonstrated **decreased overall survival** (OS) in **non-small cell lung cancer (NSCLC)** patients **with liver metastases treated with nivolumab compared to the overall pooled population treated with nivolumab** (3-year OS: 17% vs. 8%; median OS: 11.1 vs. 6.8 months, respectively)

IT efficacy in liver is limited by the unfavourable conditions of the liver: dense estroma, low rate macrophages M1/M2, increase TGF-b, VEGF and cancer associated fibroblasts (CAFs)

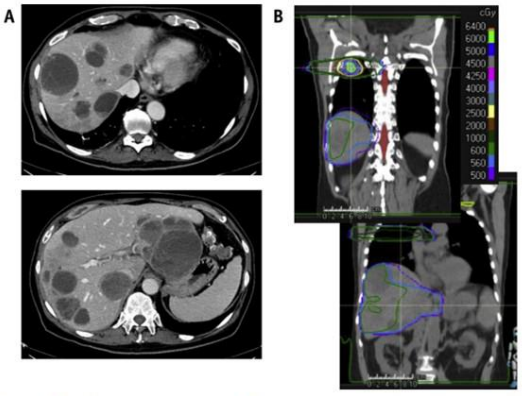
LDRT: repolarize macrophages, decrease CAFs, TGF-b and VEGF. Facilites T and NK cells infiltration and macrophages M1 stimulation.



- **LDRT Reprograms tumor microenvironment, making more easy immune system cells to go inside the tumor.**

RESULTS

- Low-dose RT to large areas of tumor burden can be safe and achieve significant responses.
- CASE:
  - Patient with **melanoma metastases in the liver, lung, bone, and brain** that **progressed during the course of 4 years on numerous chemo, targeted, and immune therapies**, yttrium-90 radioablation to 2 liver lobes, and T cell therapy presented to our clinic. Three months after T cell infusion and 1 month after resuming combined ipilimumab with nivolumab the patient continued to progress.



Four-months later, the patient achieved a partial response in liver.
No changes in liver function or hepatic/pulmonary toxicity were noted.

Fig. 3. Low-dose radiation therapy (RT) to nearly the whole liver. (A) Computed tomography with contrast before RT. (B) Low-dose RT treatment plan (coronal).

50 Gy in 4 fractions to a lung lesion and 5.6 Gy in 4 fractions to nearly the entire liver (Fig. 3B). Given the extent of disease burden (largest liver lesion measuring 9.5 cm) and the risk for radiation-induced hepatopathy, a small portion of the inferior liver was spared.

Two years after liver radiation treatment, the patient has no evidence of disease, with a durable and complete response for the liver metastases (Figure 2C).

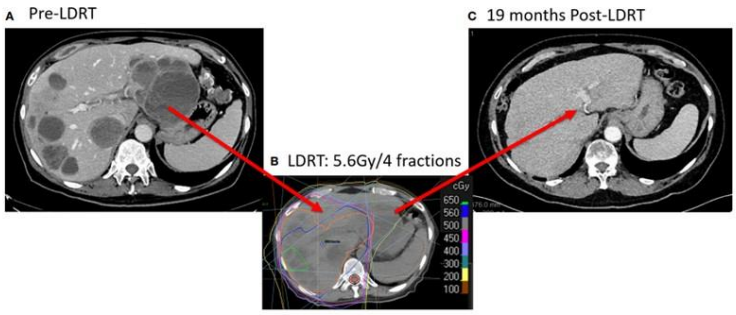


FIGURE 2 | Complete Response with LDRT to Liver metastases. **(A)** CT scanning (9/4/2019) before LDRT showed multiple liver metastases. **(B)** The patient received 50 Gy/4 fractions to a lung lesion and 5.6 Gy/4 fractions to nearly the entire liver from 10/8/2019 to 10/11/2019. **(C)** 19 months after LDRT, CT scans (4/19/2020) showed a complete response in the liver.

Hyperthermia

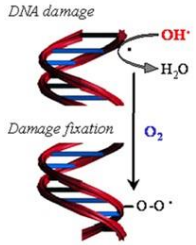
What we can do to improve?

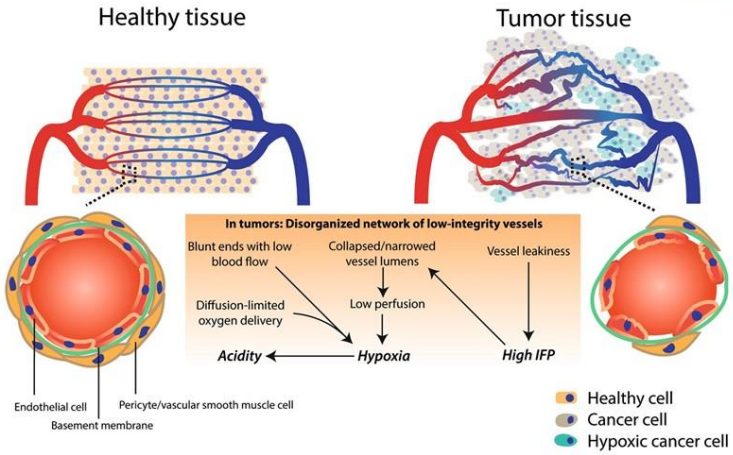
- Having a high dose to kill the tumor without damaging the patient
- Having immune system estimulation and systemic response (abscopal response)

HYPOXIA

- **90% of tumor have high grade hypoxia… specially the most agressive.**

"Oxygen enhancing effect" of RT





Cell Death & Disease (*Cell Death Dis*) ISSN 2041-4889 (online)

Hypertermia & alfa-beta

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (X)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

Abbreviations: RT: Radiotherapy; HTRT: Thermoradiotherapy; T: Temperature; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; BED: Biologically effective dose; $\%CR_{HTRT}$: % complete response with HTRT; $\%CR_{RT}$: % complete response with RT.
BED_{HTRT} and α/β_{HTRT} are estimated as described in text.
*Average dose to RT group: 68 Gy whilst to HTRT 67.5 Gy.
†Only patients with neck nodes were considered, treated with 1.5 Gy–2 Gy per fraction, 3 fractions/day.
For all LACC studies, only external RT doses were considered.

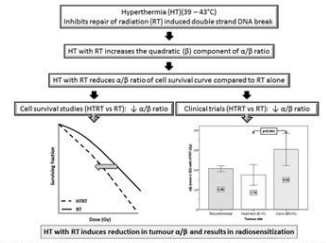


Fig. 4. Hyperthermia results in reduction in α/β values. This was evident in cell survival studies reported by Franken et al. [31] and corroborates the estimated α/β values from clinical trials of radiotherapy (RT) vs thermoradiotherapy (HTRT) in recurrent breast cancers, locally advanced head & neck cancer and locally advanced cancer cervix in the present study.

BED

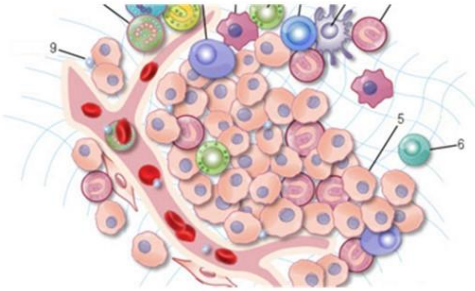
Tumor type	BED RT	BED RT + HT
Recurrent Breast	47.2Gy (39.2-57.6)	**89.2 Gy** (77.0-98.7)
LA H&N	79.1Gy (69-84)	**141.9Gy** (124.2–165.0)
LA Cervical ca	59.9Gy (48-72)	**84.2Gy** (61.7–98.5)

a/b

Tumor type	a/b RT	a/b RT+HT
Recurrent Breast	10	**1.89 a 2.15** (mean: 2.05, 95% CI: 1.90–2.22).
LA H&N	10	**1.28 a 2.58 Gy** (mean: 1.74, 95% CI: 1.29–2.19)
LA Cervical ca	10	**2.03 a 3.70 Gy** (mean: 3.03, 95% CI: 2.24–3.82)

Tumor microenvironment…

- Different cells, including immune cells inside and around tumor.
- **Has been demonstrated to have a role in tumor progression.**



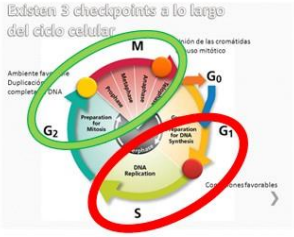
"Tumor microenvironment" is hostile to radiotherapy

- Lack of oxygen…
- **Acidity…**
- **And..**

RADIOTHERAPY AND CELL CYCLE

- **Late G2 phase** and **M** the most **radiosensitive**
- **G1 phase** and **late S** the most **radioresistant**.

How much & **when** we treat with RT matters!



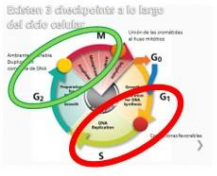
MICROENVIRONMENT also MATTERS!

HeonJoo Park, John C. Lyons, Robert J. Griffin, Byung U. Lim, and Chang W. Song "Apoptosis and Cell Cycle Progression in an Acidic Environment after Irradiation," *Radiation Research* 153(3), 295-304, (1 March 2000). https://doi.org/10.1667/0033-7587(2000)153[0295:AACCPI]2.0.CO;2

- **Relation: Apoptosis/cell cycle phase/RT dose/microenvironment in irradiation cels**
- **Different RT doses**
  - **4Gy: Apoptoses after G_2/M.**
  - **12 Gy: Some apoptosis in G_1 y S . Most apoptosis G_2/M.**

Acid pH (<7,1) apoptosis at 4 & 12 Gy supressed (difficulties in cell cycle progression towards G2/M).

- **20 Gy apoptosis in all phases.**
  - **Fast at neutral pH, low at acid pH**

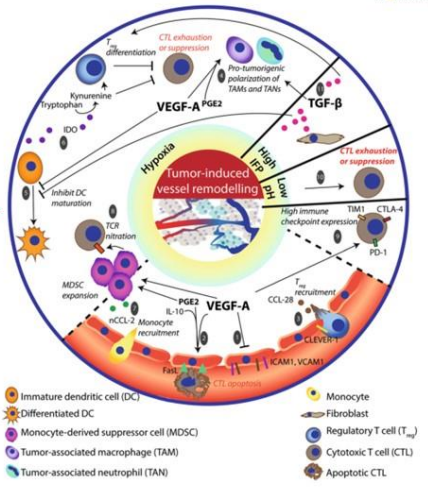


"Tumor microenvironment" is hostile to radiotherapy

- Lack of oxygen…
- **Acidity…**
- **And..**

HYPOXIA IMPORTANCE…

Dendritic cells and vaccine therapy!!!



Schaaf et al. Cell Death and Disease 20189:115

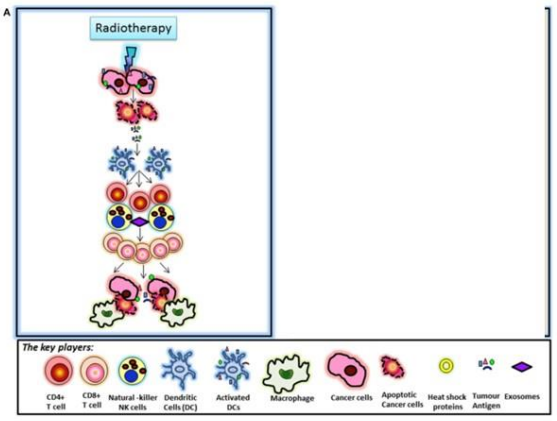
Hyperthermia

What we can do to improve?

- Having a high dose to kill the tumor without damaging the patient
- Having immune system estimulation and systemic response (abscopal response)
- Increasing oxygen
- Decreasing acidity
- "Unblocking immune system"

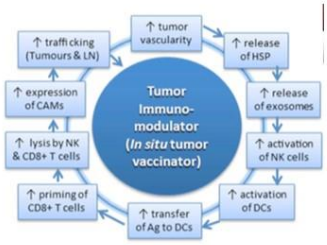
RT, HT & Immune system activation...

- **RT:**
  - Activate DC → Ag presentation → activate T cell → estimulates TCD8+ → citokines → malignant cells death → macrophages. (ABSCOPAL)



Datta NR, Kok HP, Crezee H, Gaipl US and Bodis S (2020) Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses. Front. Oncol. 10:819. doi: 10.3389/fonc.2020.00819

- **HT:**



HSP: Heat shock proteins; NK: Natural killer; DC: Dendritic cells; Ag: Antigens; CAM: Cell adhesive molecule; LN: Lymph nodes

Lymphocytes infiltration rate determines immune response

Radiotherapy/**Hyperthermia** & Immunotherapy combination

Radiotherapy & hyperthermia can convert "COLD" tumors that don't respond to immunotherapy, in "HOT" tumors with high T lymphocytes infitration more responders

Demaria, Journal of Immunotherapy of Cancer, 2022

What we need is to adapt our treatments to what we want to achieve…

- Local lethal effect.
- Systemic effect.

JAMA Oncology | Original Investigation

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

Rolf D. Issels, MD, PhD; Lars H. Lindner, MD; Jaap Verweij, MD; Rüdiger Wessalowski, MD; Peter Reichardt, MD; Peter Wust, MD; Pirus Ghadjar, MD; Peter Hohenberger, MD; Martin Angele, MD; Christoph Salat, MD; Zeljko Vujaskovic, MD; Soeren Daugaard, MD; Olav Mella, MD; Ulrich Mansmann, MD; Hans Roland Dürr, MD; Thomas Knösel, MD; Sultan Abdel-Rahman, PhSc; Michael Schmidt, MD; Wolfgang Hiddemann, MD; Karl-Walter Jauch, MD; Claus Belka, MD; Alessandro Gronchi, MD; for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00003052

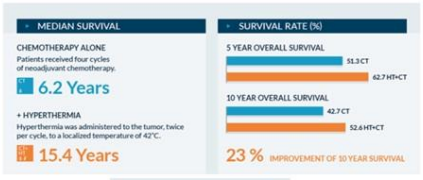
JAMA Oncol. 2018;4(4):483-492. doi:10.1001/jamaoncol.2017.4996
Published online February 15, 2018. Last corrected on April 12, 2018.

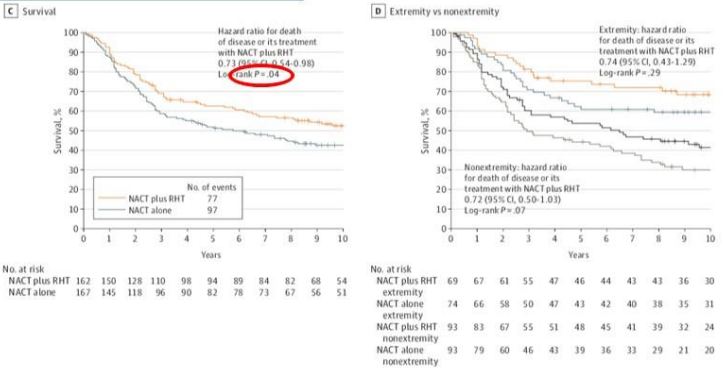
JAMA Oncology | Original Investigation

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma
The EORTC 62961-ESHO 95 Randomized Clinical Trial

OS HT+CT vs CT:

- 5 years:
  62.7% vs 51.3%, (**p = 0.04**)





A, Median local progression free survival was 5.6 years (95% CI, 2.9-8.7) in the NACT plus RHT group compared with 2.4 years (95% CI, 1.7-4.2) in the NACT-alone group. B, Median disease-free survival was 2.8 years (95% CI, 2.0-4.9) in the NACT plus RHT group compared with 1.5 years (95% CI, 1.1-2.1) in the NACT-alone group. C, Median survival was 15.4 years (95% CI, 6.6 to >17.0 [the upper confidence limit cannot be estimated and represents the lower bound for the value to be expected]) in the NACT plus RHT group compared with 6.2 years (95% CI, 3.2-10.3) in the NACT-alone group. D, Extremity tumor-survival rates at 5 and 10 years were 75.2% and 68.3% in the NACT plus RHT group compared with 60.8% and 59.2% in the NACT-alone group. The absolute difference at 5 years was 14.4% (95% CI, 0%-29.5%) and was 9.1% (95% CI, 0%-24.7%) at 10 years. Nonextremity tumor-survival rates at 5 years and 10 years were 53.5% and 41.3% in the NACT plus RHT group compared with 44.0% and 29.9% in the NACT-alone group. The absolute difference at 5 years was 9.5% (95% CI, 0%-23.8%) and was 11.4% (95% CI, 0%-25.1%) at 10 years. NACT indicates neoadjuvant chemotherapy consisting of doxorubicin, ifosfamide, and etoposide; RHT, regional hyperthermia.

European Journal of Cancer 158 (2021) 123–132

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

Rolf D. Issels [a,*,1], Elfriede Noessner [b,1], Lars H. Lindner [a], Michael Schmidt [c], Markus Albertsmeier [d], Jean-Yves Blay [e], Emanuel Stutz [f], Yujun Xu [g], Veit Buecklein [a], Annelore Altendorf-Hofmann [h], Sultan Abdel-Rahman [a], Ulrich Mansmann [g], Michael von Bergwelt-Baildon [i], Thomas Knoesel [j]

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[c] Munich Cancer Registry, Institute of Medical Information Processing, Biometry and Epidemiology, LMU, Munich, Germany
[d] Department of General, Visceral and Transplantation Surgery, LMU Munich, Munich, Germany
[e] Department of Medicine, Centre Leon Berard, 28 Rue Laennec1, Lyon, 69373, France
[f] Dept. of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern Freiburgstr.18, Switzerland
[g] Institute of Medical Informatics, Biometry and Epidemiology (IBE), LMU Munich, Germany
[h] Department of General, Visceral and Vascular Surgery, University Hospital Jena, Germany
[i] Deutsches Konsortium für Translationale Krebsforschung, Bayrisches Zentrum für Krebsforschung, and Comprehensive Cancer Center LMU, Munich, Germany
[j] Institute of Pathology, LMU, Thalkirchner Str.36, Munich, 80337, Germany

Received 31 July 2021; received in revised form 6 September 2021; accepted 10 September 2021
Available online 16 October 2021

- The study protocol included an optional accompanying **translational program, to determine immune cells of tumour tissue.**

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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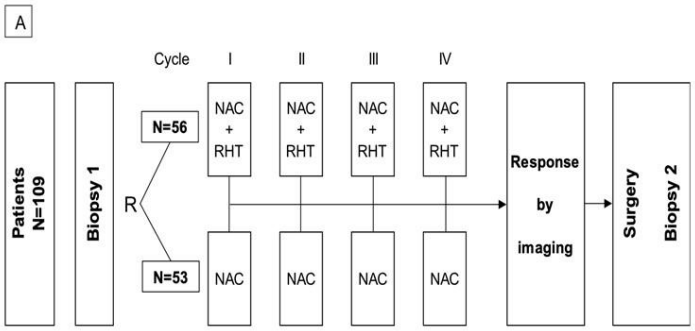

- **28 patients had paired samples** (only available for patients who had been biopsied and finally operated at the Munich Centre).
  - NAC-RHT: 13
  - NAC: 15

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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- Examined for **TILs (Infiltrating tumor lymphocytes)** and immune biomarker expression, including **CD8, PD-1, PD-L1, and FOXP3.**
  - The TIL score was assigned as high (>5 cells per HPF) or low (5 cells per HPF).
  - The CD8 cell score was defined by anti-CD8 antibody immunoreactivity as high (>10 cells per HPF) or low (<10 cells per HPF)

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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- Compared the tumour-associated immune infiltrate between **NAC-RHT and NAC treatment at baseline (biopsy 1) and after pre-operative therapy (biopsy 2)**
- As seen in paired samples, **the immune infiltrate** in post- treatment biopsies of the NAC-RHT and the NAC groups **showed comparable distributions of**:
  - high TIL tumours (46.2%; 6/13 versus 53.3%; 8/15)
  - high CD8 tumours (33.3%; 4/12 versus 45.5%; 5/11)
  - tumours with PD-1pos cells (33.3%; 4/12 versus 38.5%; 5/13),
  - FOXP3pos cells (0%; 0/13 versus 6.7%; 1/15)
  - PD-L1pos tumour cells (0%; 0/13 versus 6.7%; 1/15).

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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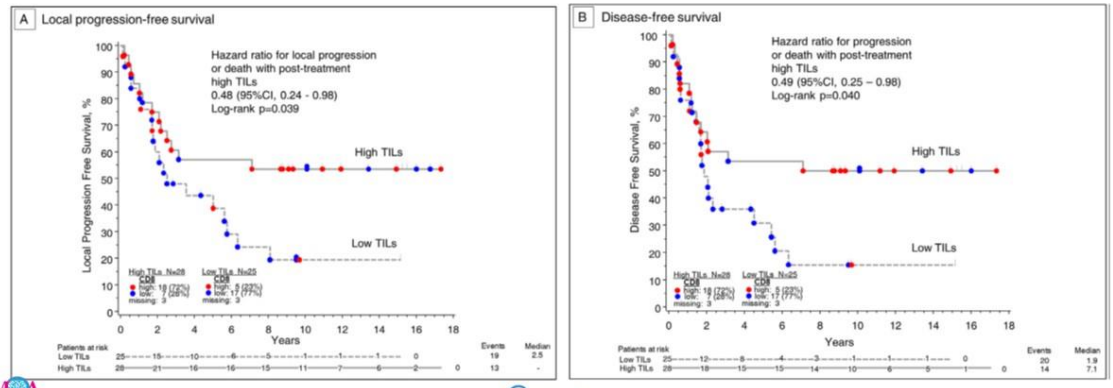
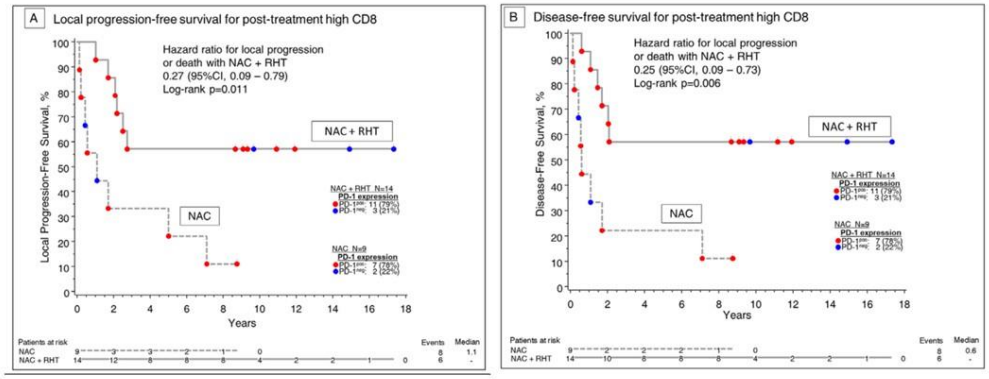
- In post-treatment samples (biopsy 2): **53%** (28/53) tumours **high TIL infiltrate** *vs* 47% (25/53) with low TIL infiltrate.
- **High TILs significantly associated with prolonged LPFS (p 0.039) and DFS (0.040)**

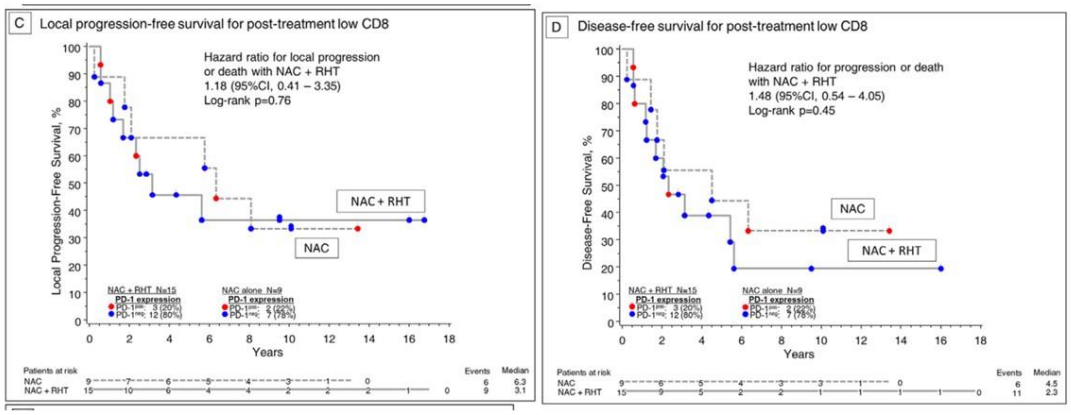


High CD8 by groups



Patients of the NAC-RHT group, whose tumours exhibited high CD8 counts, had significantly longer LPFS (p=0.011) and DFS (p =0.006) compared to the NAC group.

Low CD8 by groups



CONCLUSIONS

- **Preoperative chemotherapy +/- concomitant Hyperthermia turned the state of a cold, non-immunogenic sarcoma into a more immunogenic tumour** with high TILs, a decrease of immune-suppressive FOXP3 regulatory Tcells, and absence of PD-L1 expression.
- In patients with **high increase in CD8, the addition of hyperthermia significantly increased local progression free survival and disease free survival.**

Immune effect of hyperthermia

We need to increase CD8 and then… hyperthermia
How we increase CD8?

QT, RT, IMMUNOTHERAPY, HYPERTHERMIA

> Oral Oncol. 2012 Jul;48(7):594-601. doi: 10.1016/j.oraloncology.2012.01.024. Epub 2012 Feb 21.

Radiochemotherapy induces a favourable tumour infiltrating inflammatory cell profile in head and neck cancer

M Tabachnyk [1], L V R Distel, M Büttner, G G Grabenbauer, E Nkenke, R Fietkau, D Lubgan

Affiliations + expand

PMID: 22356894 DOI: 10.1016/j.oraloncology.2012.01.024

> Ann Surg. 2018 Dec;268(6):992-999. doi: 10.1097/SLA.0000000000002410.

The Dynamic and Transient Immune Microenvironment in Locally Advanced Esophageal Adenocarcinoma Post Chemoradiation

Ronan J Kelly [1], Ali H Zaidi [2], Matthew A Smith [3], Ashten N Omstead [2], Juliann E Kosovec [2], Daisuke Matsui [2], Samantha A Martin [2], Christina DiCarlo [3], E Day Werts [4], Jan F Silverman [3], David H Wang [5], Blair A Jobe [2]

Clinical Trial > Br J Cancer. 2019 Sep;121(6):490-496. doi: 10.1038/s41416-019-0541-3. Epub 2019 Aug 7.

Alteration in tumoural PD-L1 expression and stromal CD8-positive tumour-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer

Kazue Yoneda [1], Taiji Kuwata [1], Masatoshi Kanayama [1], Masataka Mori [1], Toshinori Kawanami [2], Kazuhiro Yatera [2], Takayuki Obuuri [3], Masanori Hisaoka [4], Toshiyuki Nakayama [5], Fumihiro

Observational Study > Int J Radiat Oncol Biol Phys. 2018 Nov 1;102(3):593-600. doi: 10.1016/j.ijrobp.2018.06.404. Epub 2018 Jul 12.

Kinetics of Intratumoral Immune Cell Activation During Chemoradiation for Cervical Cancer

Stephanie Dorta-Estremera [1], Lauren E Colbert [2], Sita S Nookala [1], Ananta V Yanamandra [1], Guojun Yang [1], Andrea Delgado [2], Megan Mikkelson [2], Patricia Eifel [2], Anuja Jhingran [2], Lin L Lille [2], James Welsh [2], Kathleen Schmeler [3], Jagannadha K Sastry [1], Ann Klopp [4]

Randomized Controlled Trial > Anticancer Res. 2014 Nov;34(11):6505-13.

Effect of neoadjuvant chemoradiation on tumor-infiltrating/associated lymphocytes in locally advanced rectal cancers

Stephanie H Lim [1], Wei Chua [2], Christina Cheng [3], Joseph Descallar [4], Weng Ng [2], Michael Solomon [5], Les Bokey [6], Karen Wong [7], Mark T Lee [8], Paul de Souza [9], Joo-Shik Shin [10], Cheok Soon Lee [11]

Breast cancer with multiple brain metastases – Hypofractionated RT

- **30Gy in 5 fx RT concomitant with 3 fx Hyperthermia**
- **3 Hyperthermia fx in monotherapy**

Red – Only RT
Red and green – RT + HT
Green – Only RT

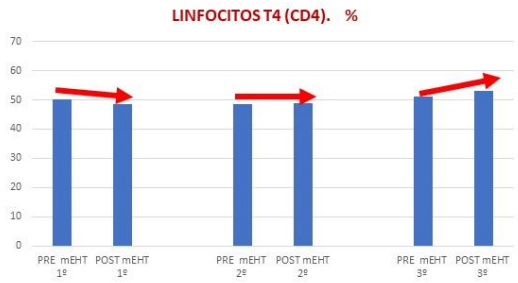
enero

L	M	X	J	V	S	D
26	27	28	29	30	31	1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31	1	2	3	4	5

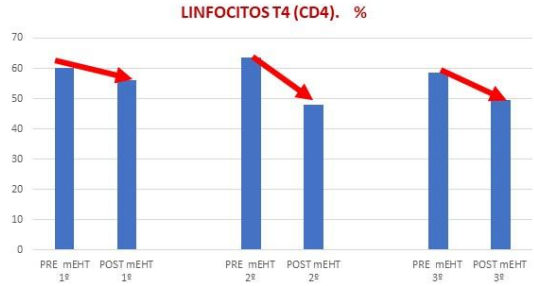
- **Analyze peripheral blood level of lymphocytes just before & after each hyperthermia treatment**

Breast cancer with multiple brain metastases–Hypofractionated RT

- RT + Hyperthermia



Hyperthermia in monotherapy

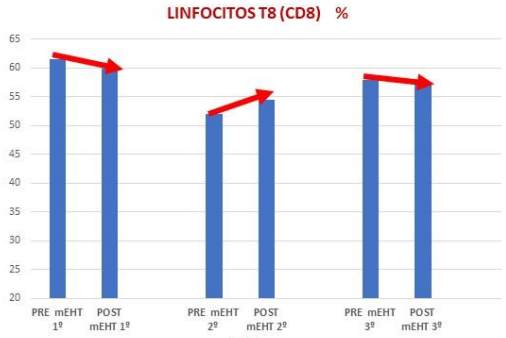


Red – Only RT
Red and green – RT + HT
Green – Only RT

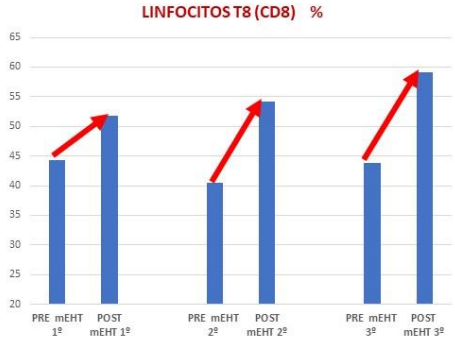
T CD4⁺ decrease → favorable prognosis

Breast cancer with multiple brain metastases – Hypofractionated RT

- RT + HT



Hyperthermia in monotherapy



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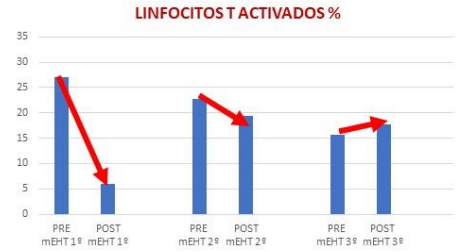
NK, activated T lymphocythes & TCD8⁺ increase-> improves prognosis

Breast cancer with multiple brain metastases – Hypofractionated RT

- RT + HT

Hyperthermia in monotherapy



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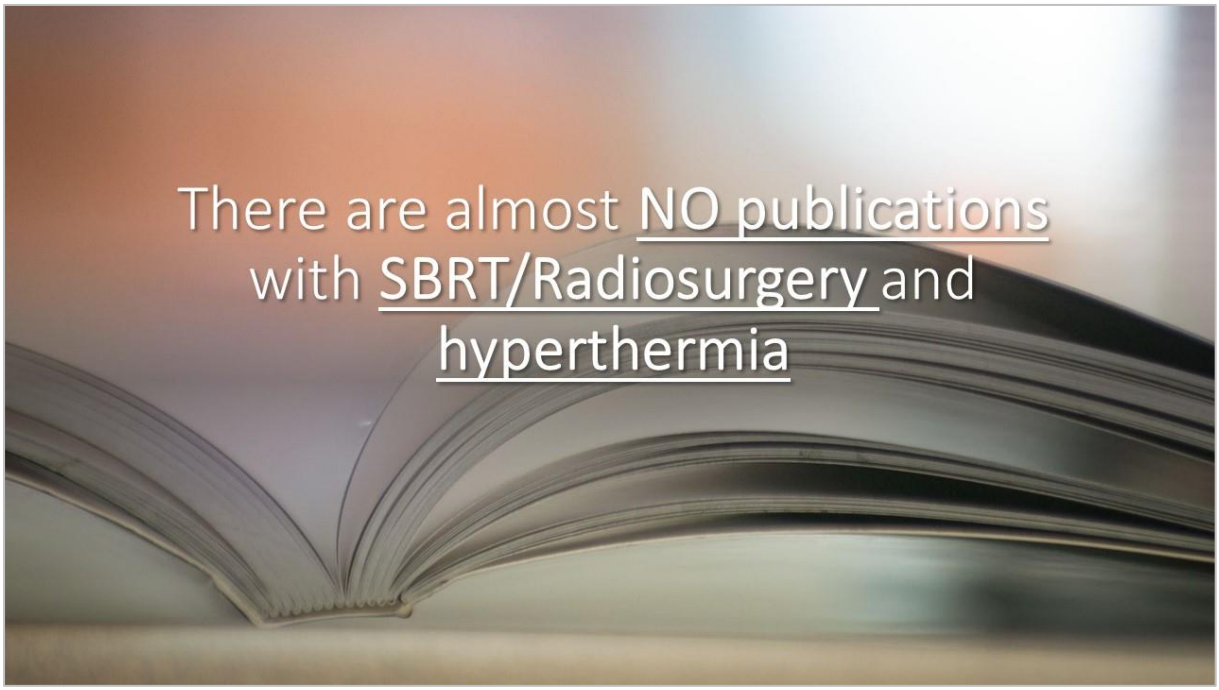


We have published the ”first abstract” combining Radiosurgery/SBRT + mEHT…

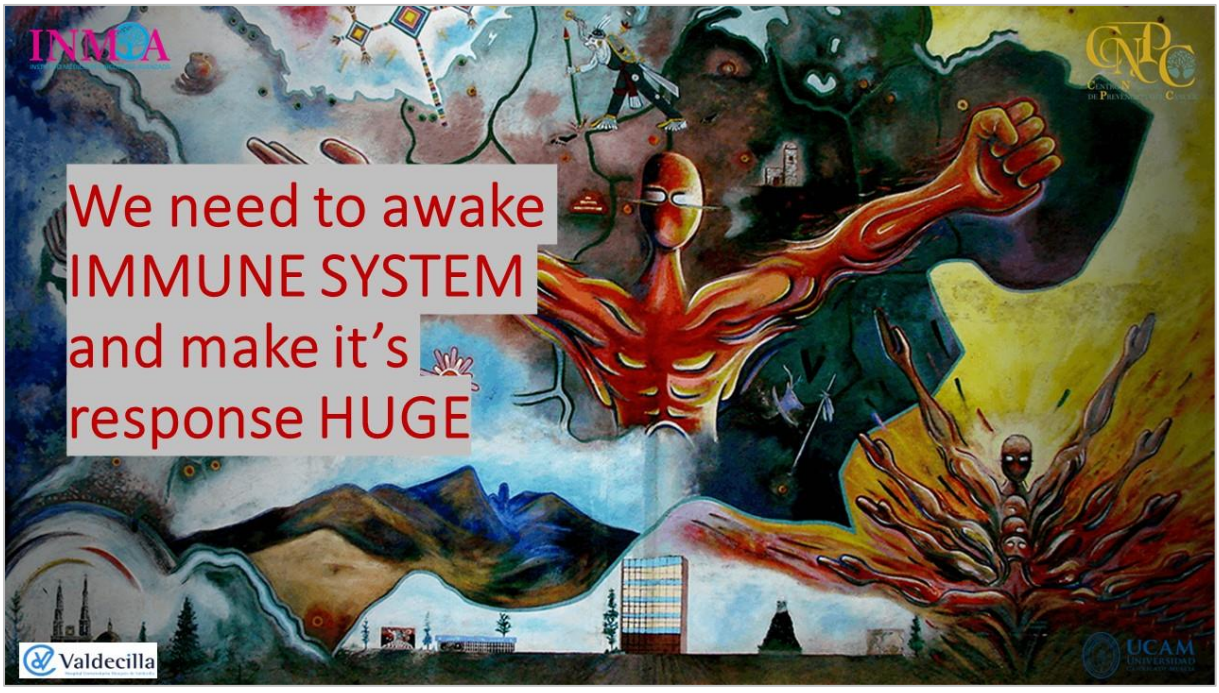
Increase Radiosentivity

Increase Abscopal

International Radiosurgery Congress NY 2024

Reirradiation High Grade Glioma with RS+mEHT (No options...)

- **8 patients with 14 lesions that received GRS and mEHT between** April 2023 and November 2023 were prospectively included.
- Median age of 48 years (range 30-62 years)
- Median of 2 lesions (range 1-3) underwent GRS and mEHT during the study period.
- Tumor progression after standard Stupp protocol and 3 patients had a previous second course of radiation.
- The median time from previous radiation was 11 months (range 21 – 6 months).
- The median (2.8cm³), minimum (0.2cm³), and maximum PTV volume (51cm³). 57% (n = 8) of the lesions were treated in 1 fraction, 29% (n = 4) in 5 fractions and 14% (n = 2) in 3 fractions. **Median dose in 1 fraction was 15 Gy** (range 15 - 18 Gy). Lesions treated in **5 fractions received 25 Gy or 30 Gy** and lesions treated in **3 fractions received 24 Gy.**
- **Overall survival at 6 months was 67%.** Acute and subacute treatment tolerance was acceptable, all patients needed ambulatory steroid medication adjustment.
- **Conclusion**: **High grade glioma reirradiation with GRS in combination with mEHT showed a favourable impact in local control and overall survival with low toxicity**. Longer follow-up and larger series is needed to validate these results.



SBRT in polimetastases

Advances in Radiation Oncology (2021) 00, 100734

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Can Polymetastatic Disease Be ARRESTed Using SABR? A Dosimetric Feasibility Study to Inform Development of a Phase 1 Trial

Mark T. Corkum, MD, MSc,[a] Hatim Fakir, PhD,[b] David A. Palma, MD, PhD,[a] Timothy Nguyen, MD,[a] and Glenn S. Bauman, MD[b,c]

[a]Division of Radiation Oncology, Department of Oncology; [b]Department of Medical Biophysics, London Health Sciences Centre, London, Ontario, Canada

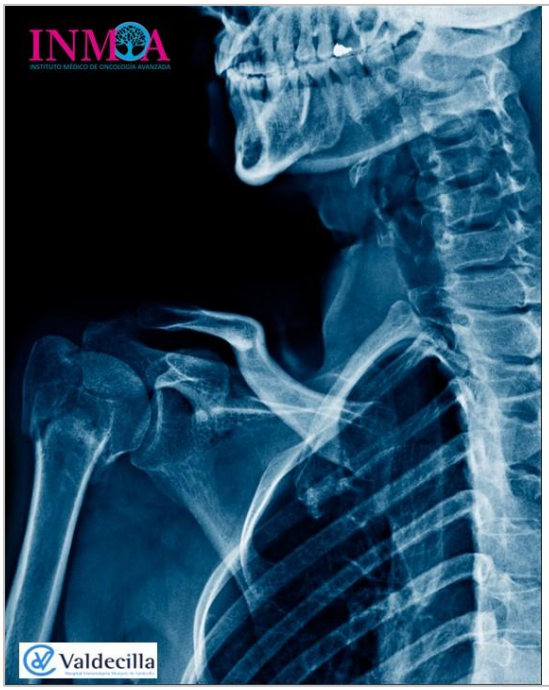
Received December 14, 2020; accepted May 21, 2021

Phase I ARREST trial
- Patients with > 10 metastases
- No available systemic treatment option

De-escalation dose level
- Dose level 0: 6Gy × 1 fraction to all sites in 1 week.

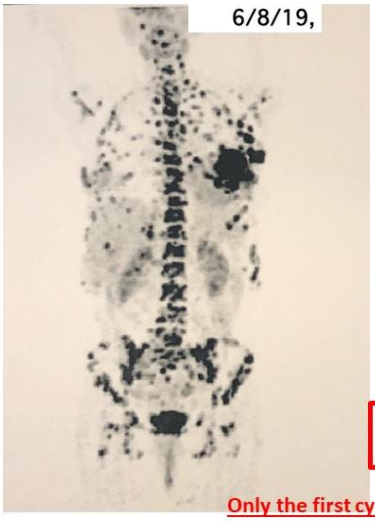
Escalation dose levels
- Dose level 1: 6Gy × 2 fractions to all sites in 2 weeks.
- Dose level 2: 6Gy × 3 fractions to all sites in 3 weeks.
- Dose level 3: 6Gy × 4 fractions to all sites in 4 weeks.
- Dose level 4: 6Gy × 5 fractions to all sites in 5 weeks.

Valdecilla *orkum, Advances in Radiation Oncology ,2021*



One of our cases…

- 48yo man
- Primary tumor: colon cancer
- **15 lung metastases & 2 liver metastases**
- No options for more chemotherapy
- IK 90%
- **Treatment:**
  - **SBRT to each of the lung metastases**
  - **SBRT to each of the liver metastases**
  - **+ mEHT to both locations.**
- **18 months later stable disease.**
- **No significant toxicities**



6/8/19,

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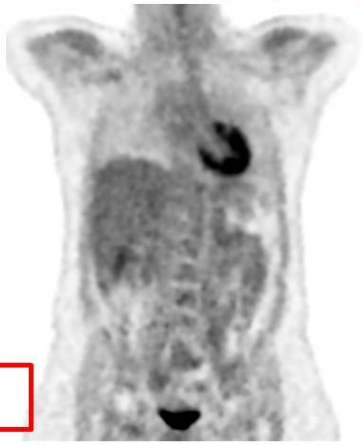


Breast cancer

4* CT cycles
29 mEHT treatments

2.5 months later
COMPLETE RESPONSE

Only the first cycle with paclitaxel + pertuzumab + trastuzumab.

The other ones only pertuzumab + trastuzumab (patient desirees)

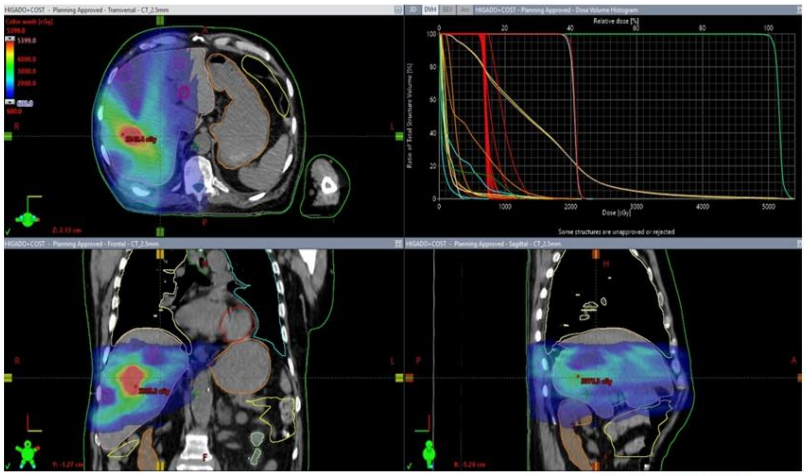
CLINICAL CASE

Male, 62yo
Stage IV prostate cancer, Gleason 9 (4+5) diagnosed in 2013.
Multiple treatments: radiotherapy, Abiraterone, Enzalutamide, Docetaxel...)

On february 2022:

Multiple bone metastases (skull, spine, pelvis, escapula, ribs...)
14 liver metastases on MRI
No options for systemic treatment

RT + HYPERTHERMIA as a “local-systemic” treatment.

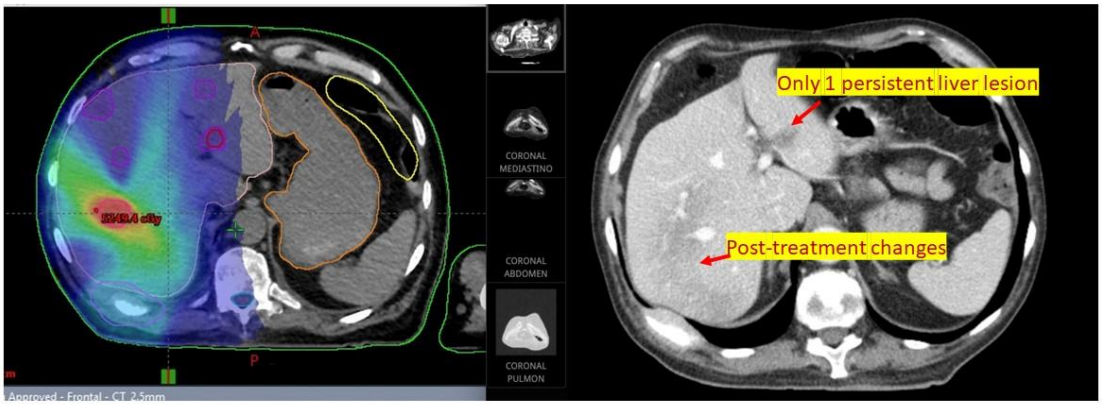


- 13 liver metastases treated with 5 fractions of 1.4Gy
- 1 liver metastases treated with 5 fractions of 10 Gy

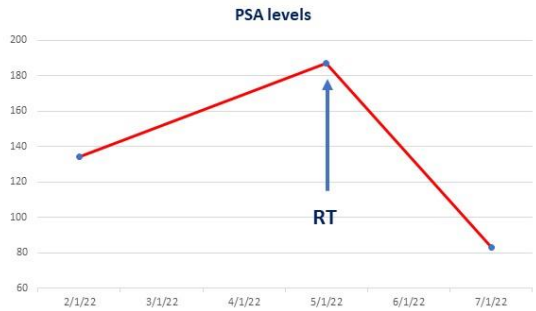
Concomitant mEHT (3 times a week, 60 minutes per treatment)

RESULTS

2 months after RT + mEHT treatment



RESULTS



No toxicities from treatment

Patient lived without systemic treatment for 15 months more with Good QoL...

CLINICAL CASE

Male, 42 yo
Local Adenocarcinoma of pancreas in 2019

→ Surgery
→ Relapse → Folfirinox
→ Progression → Gemcitabine-Abraxane
→ Radiofrequency of 3 liver metastases
→ Progression → Clinical Trial immunotherapy
→ Progresion → Folfirinox → Partial response but persistent disease.

CLINICAL CASE

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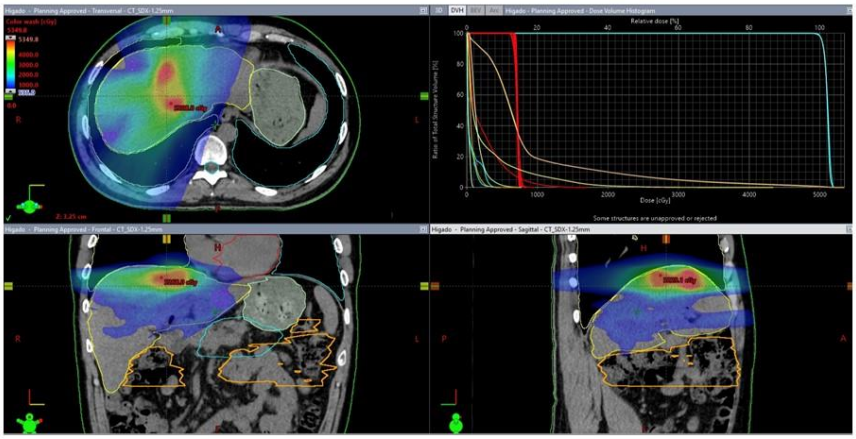
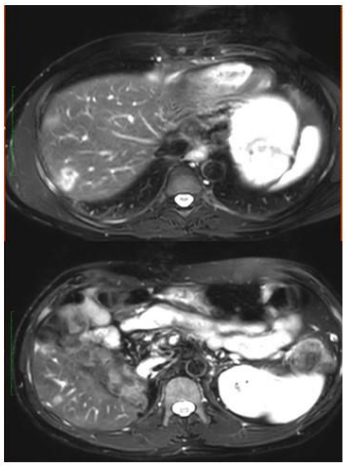
TREATMENT

RT:
- **Pancreas: 45Gy in 25 fractions**
- **Liver metastases:**
  - **2 treated with 5 fractions of 10Gy (50Gy)**
  - **9 treated with 5 fractions of 1.4Gy (7Gy)**

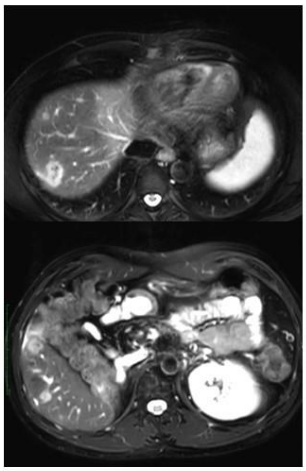
HYPERTHERMIA to liver and pancreas: three times a week during RT. 60 minutes treatment



- MRI 9 weeks after treatment:
  - Complete response of pancreatic tumor.
  - Stable disease of most of liver lesions. Minimum increase in two.



MRI before treatment



MRI 9 weeks after treatment

Lived for 12 months more without systemic treatment and Good QoL

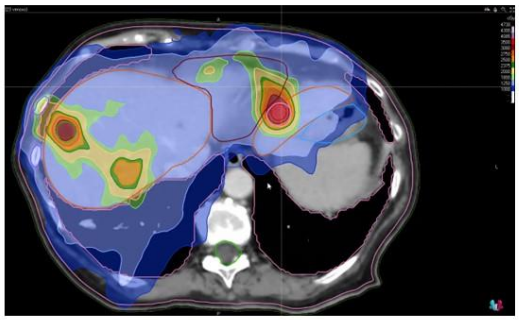
Died from peritoneal infection

Metastatic melanoma

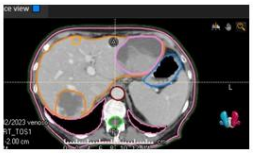
Progresion after immunotherapy

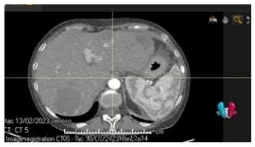
No options for treatment

PTV liver= 10 Gy (5 x 2 Gy)
PTV left lobe metastases= 25 Gy (5 x 5 Gy)
Boost Lattice lef lobe= 18 Gy
Boost to >10 metastases: 18 Gy



February 2023 April 2023

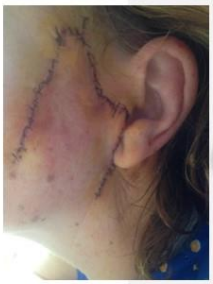


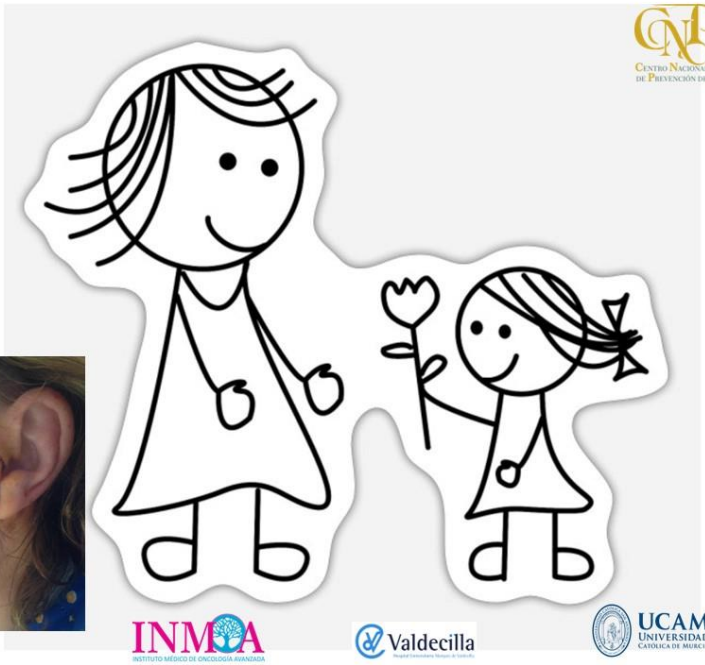


Stable disesease
Still alive
Now with Nivolumab

My mum

55yo Melanoma in cheek
T3N0M0
No adjuvant treatment
December 2015





My mum

June 2018 brain metastases
Surgery
Radiosurgery

September 2018: 4 more metastases
4 types of immunotherapy
Almost death for side effects

March 2019 no options for treatment

What I did?

RT to every lesion in single dose + mEHT

My mum now...

- More than 12 distant metastases...
- Some >7cm
- Free of disease

Muchas gracias

More than 2500m2...
2 clinics (Madrid and Bilbao)

First Cancer Prevention Center in Europe

CONCLUSIONS

- The key of cancer cure is immune system
- Radiotherapy is a very powerful tool to kill malignant cells locally but also to stimulate immune system (abscopal effect).
- Hyperthermia is a very powerful tool to increase radiotherapy, chemotherapy and immunotherapy effect not only locally, but also sistemically as it also stimulates immune system (abscopal effect).
- Oncological treatment combination is the key to have a Good tumor control and survival without significant side effects.
- More research is needed...

Valdecilla Cantabria, España

CNPC Centro Nacional de Prevención del Cáncer

INMOA Instituto Médico de Oncología Avanzada

Madrid
Bilbao

UCAM Universidad Católica de Murcia

Thank you!!! earrojo@inmoa.es