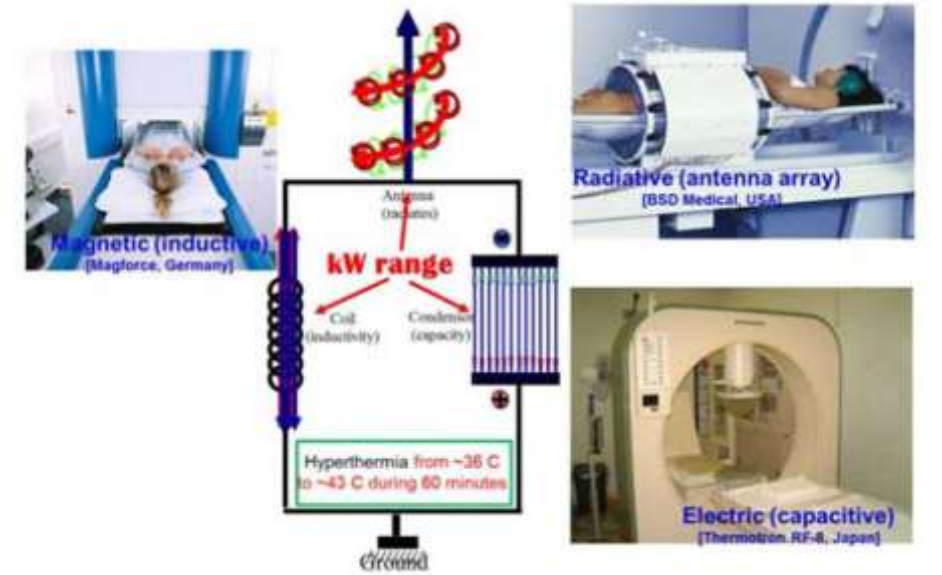
EU Scientific Seminar 2023
Radiation protection Issues in modern external beam radiotherapy
European Convention Center Luxembourg , 21 November 2023

Combined radiotherapy with hyperthermia

Alessandro Lascialfari
Dipartimento di Fisica, Università degli Studi di Pavia, INFN and INSTM, Pavia, Italy



ASSOCIAZIONE ITALIANA di FISICA MEDICA e SANITARIA

Outline

* Hyperthermia, mild hyperthermia and thermo-ablation
* Thermotheraphy combined with radiotherapy or chemotherapy

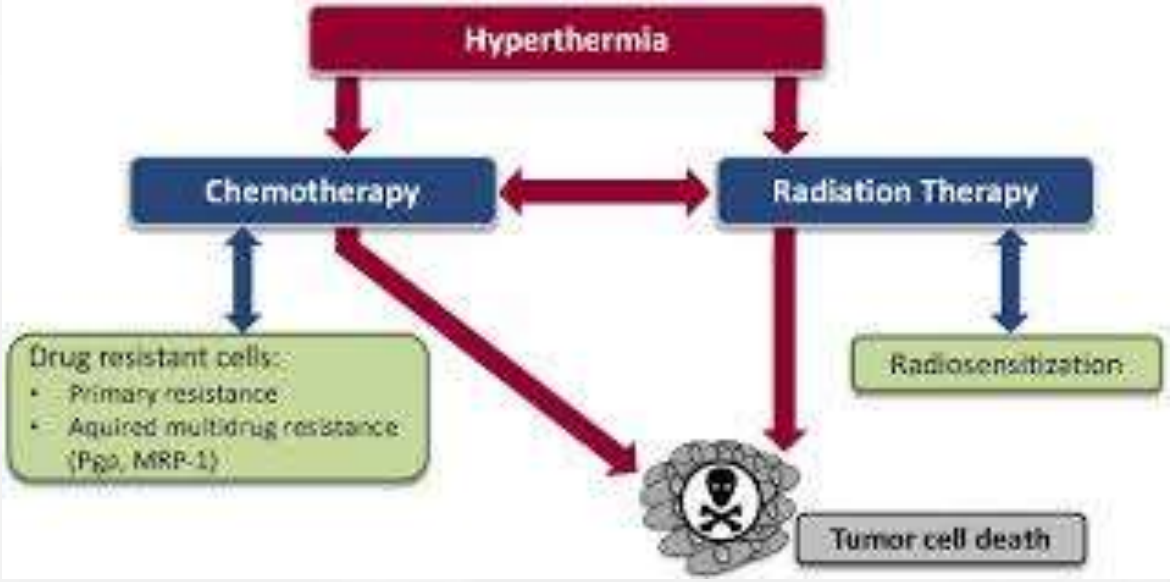
…. THE TALK **will not be exhaustive**

(and, a huge preclinical world will not be presented)

Magnetic fluid hyperthermia (MFH)

Cancer Treatment Options

- Surgery
- Chemotherapy
- Radiation Therapy

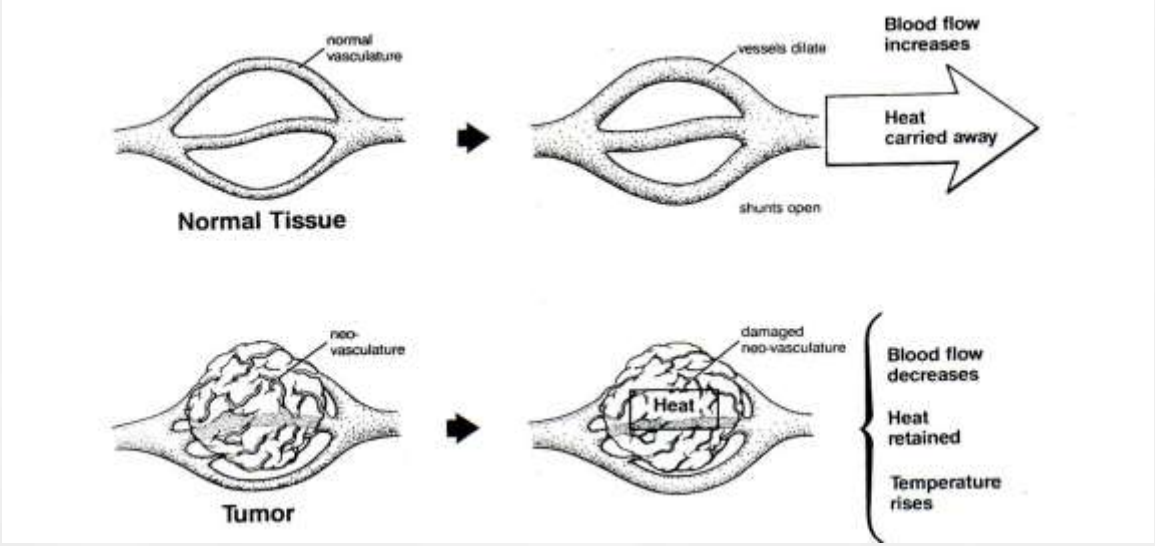


- others (immunotherapy, hormone therapy, molecular drugs….)
- Hyperthermia

In most cases, a **COMBINED therapy** is more effective

What is hyperthermia?

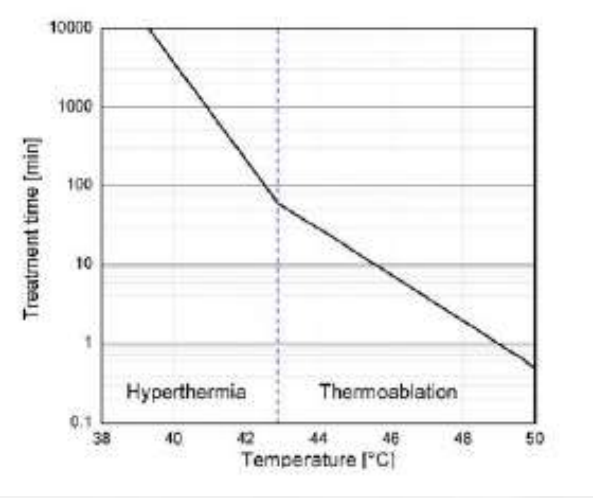
- **Hyperthermia : rise in temperature of body tissues**, globally or locally
- **Almost always used with other forms of cancer therapy**, (radiation therapy and chemotherapy)
- Documented **clinical evidence of tumor regression**
- **Biologic rationale** AND **promising** results **from lab** experiments.

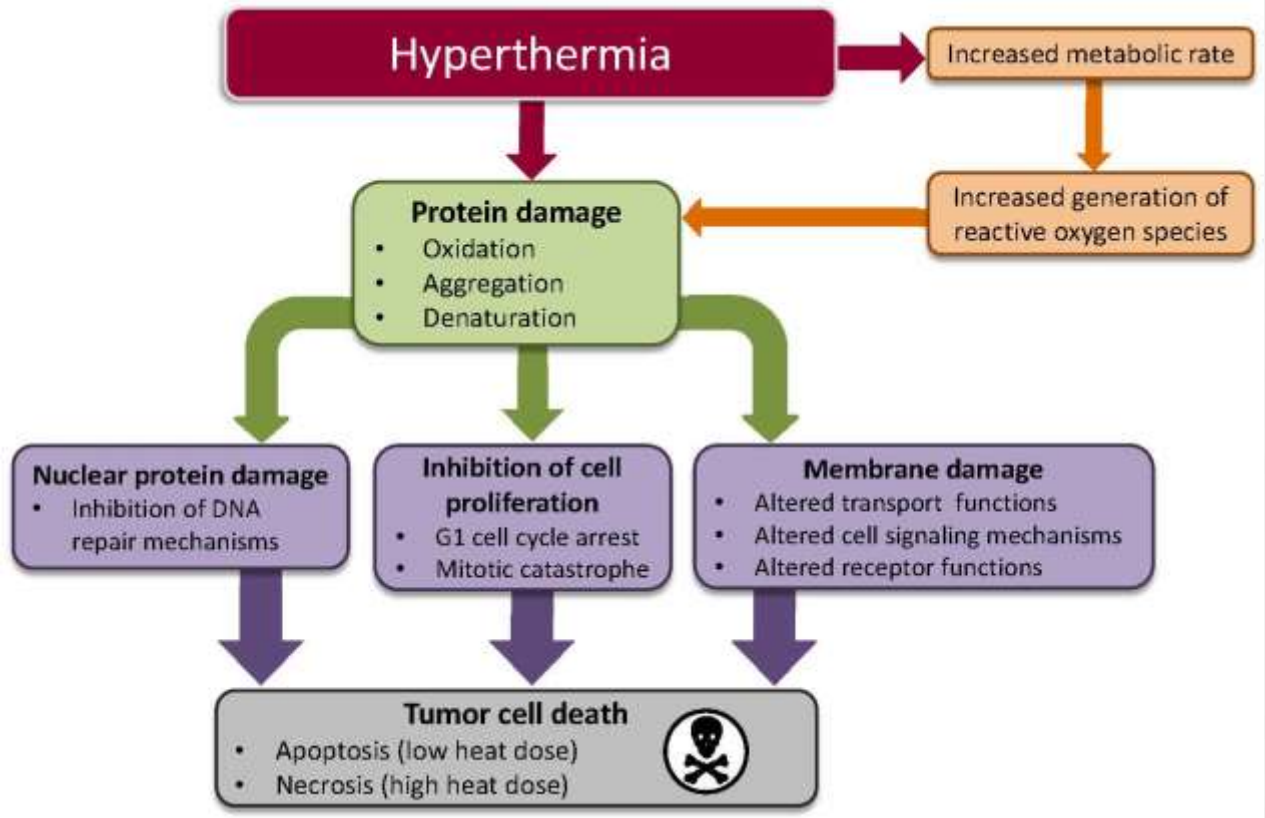


Hyperthermia and thermal ablation

• **HYPERTHERMIA**: smaller temperature rises, usually to 40 ÷ 45°C (till 41°C is "**mild**"): damage like **apoptosis**, **leading to** subsequent **cell death**. **Other effects** : activation of immunological responses, enhancement of tumor blood flow and oxygenation via greater vascular perfusion and permeability.

• **THERMOABLATION**: temperature is raised to > 50°C (**cause immediate cellular death**, through necrosis mediated by irreparable coagulation of proteins/other biological macromolecules)





Hyperthermia techniques

Mainly used heating sources:

1. Microwaves (433 to 2450 MHz, also MNPs !!), superficial
2. Radiofrequency (100 KHz to 150 MHz), deeper
3. Focused ultrasounds - **HiFU**
4. Magnetic Fluid Hyperthermia - **MFH** *(& capacitance Hyperthermia)*
5. Infrared radiators, lasers
6. Hot water/drug/blood perfusion from outside
7. Whole body in heated chambers/ blankets wrapped

Heating by **microwave and radiofrequency sources**

- good localization at shallow depths
- at greater tumor depths, even with lowered frequency, the localization is much poorer

Heating by ultrasound sources **- HiFUS**

- good penetration and temperature achieved in soft tissues
- bone or air cavities causes distortions of the heating pattern

Cancers treated with hyperthermia

1. Technique not widely available

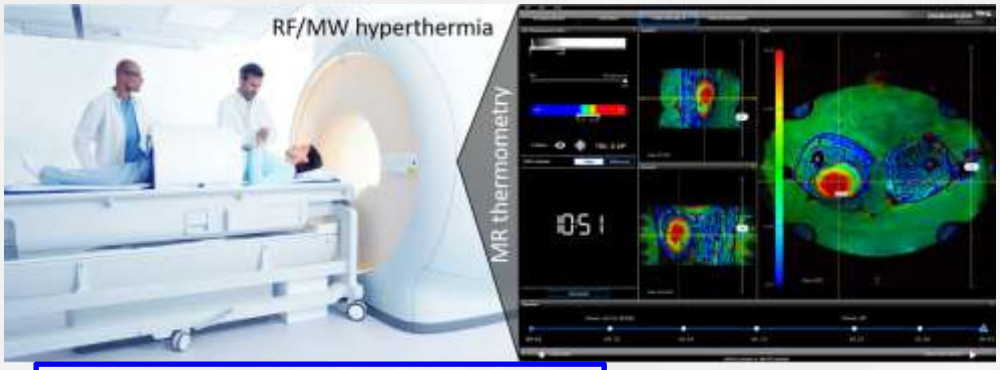
2. At some centers used, along with radiation therapy and chemotherapy, on :

- *appendix cancer*
- *bladder*
- *brain cancer*
- *breast*
- *cervical cancer*
- *esophageal cancer*
- *head and neck cancer*
- *liver*
- *lung cancer*
- *melanoma*
- *mesothelioma*
- *sarcoma*
- *rectal cancer*

Problem of temperature measurement !!

Hyperthermia Cancer Institute

Santa Monica, CA



NIH National Cancer Institute

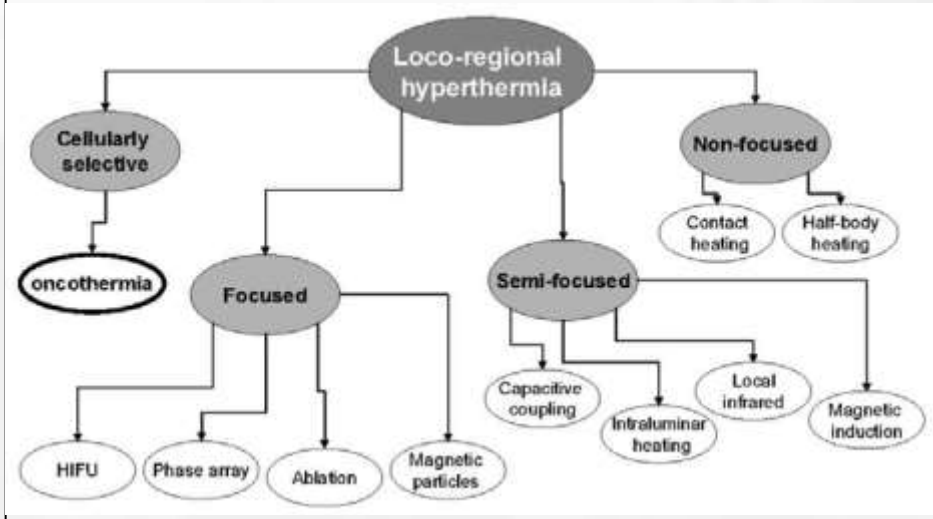
Three kinds of hyperthermia

Local hyperthermia

- Relatively **small tumors** (≤3 cm up to 5–6 cm), **superficial** or within an available **body cavity** (rectum, esophagus)
- Superficial, intraluminal applicators of different shapes and types (e.g., waveguide, spiral, and current sheet) positioned on the surface of superficial tumors with a contacting layer (bolus)
- They emit **microwaves, radio waves, HiFU, MFH** to convey heat to the tumors

Regional hyperthermia

- Large parts of the body : pelvis, abdomen, thighs
- **Perfusion Hyp** : part of patient's blood removed, heated, pumped back into limb/organ, with drugs
- Hyperthermic intraperitoneal chemotherapy (HIPEC) to treat cancers within the peritoneal cavity (primary peritoneal mesothelioma, gastric cancer)
- Tissue temperature inside the cavity to 41–42 °C



Whole body hyperthermia (WBH)

- Either radiation heat or extracorporeal technologies: the whole body T at least at 41 °C
- Typical method : immersion in a hot water bath and radiant heat with ultraviolet radiation Heat is superficially applied also using hot blankets, inductive loops, or thermal chambers

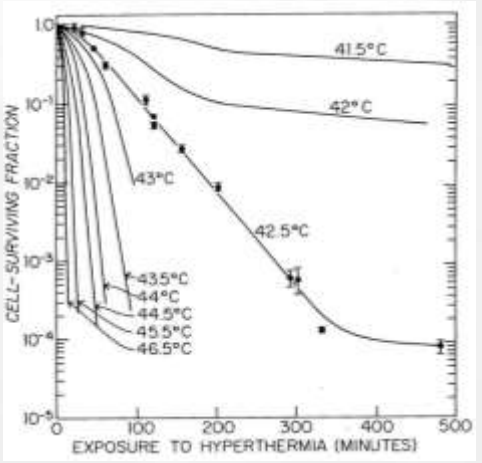
Thermal dose and TID

Preliminary observations

- Thermal dose concept for Hyp treatment widely **under debate** in literature
- Hyp temperatures are heterogeneous and show variations during treatment

Thermal dose and Thermal isoeffect dose

- **Cumulative equivalent minutes** at treatment T=43 °C achieved within 90% of the tumor volume **CEM43T90**
- Goal of action : a thermal dose of 10 CEM43T90 (or more)
- Reaching goal (time of 10 minutes or more) ⇒ doubling response & period of answer to Hyp and RT versus RT alone
- Radiation Therapy Oncology Group (RTOG) guidelines (thermometry, CEM calculations, declaration of Hyp quality)
- **Thermometry** in tumors is invasive **!!** MRI proposed as a non-invasive system
- **Thermal isoeffect dose (TID)** to compare Hyp exposures : TID modifies a given thermal dose into CEM43
- ΔT = 1 °C temperature decrease in the T-range 42.5-47 °C rewarded by doubling the prescription time (R =2)
- At less than 42.5 °C the heat exposure must be elongated even more (R = 4)



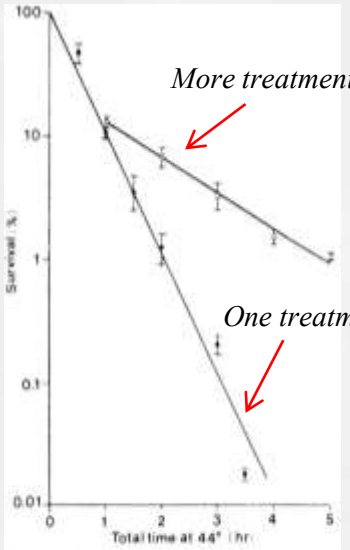


Figure 28.4. Development of thermotolerance in HeLa cells. *Closed circles* indicate cell survival to single heat exposures; *open circles* indicate response of cells treated at 44°C for 1 hour, returned to 37°C for 2 hours, and given second graded doses of 44°C for graded times. (From Gerner EW, Schneider MJ. Induced thermal resistance in HeLa cells. Nature 256:500–502, 1975, with permission.)

Hyperthermia combined with RT/ChT. I

Combination with RT

- Hyp alone not sufficient to kill cancer cells (problem of homogeneous heating)
- BUT : Hyp can improve the cell-killing effect of cytotoxic drugs and radiation (thermal chemo-sensitization and thermal radio-sensitization)
- Hyp can improve the efficiency of a given dose without supplementary toxicity
- Hyp and radiation can be synergistic or additive : synergy appears most pronounced in S-phase cells (usually resistant to radiation alone)
- Thermal enhancement ratio (TER) : defines the amount of thermal radiosensitization by quotient of the survival fraction after RT alone and in combination with Hyp

Combination with chemotheraphy

- Clinical reports : chemotherapy achieves good results in patients with body T~39°C
- Moderate Hyp (42–45 °C) improves the cytotoxicity of chemotherapeutic drugs
- Hyp and chemotherapy present synergistic anticancer effects

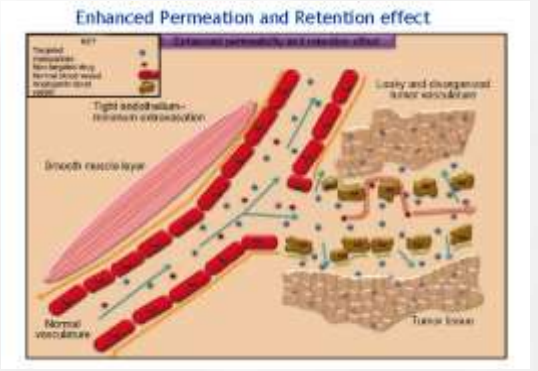
Hyperthermia combined with RT/ChT. II

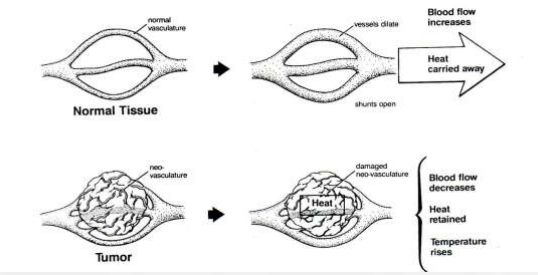
Some more observations

- Hyp + radiotherapy : breast cancer, melanoma, glioblastoma, head&neck and cervical cancer increases complete response and survival rates
- Attention : higher temperatures cause scorching, burns, pain or necrosis
- Hyp alone ⇒ inflammation of heated tissue and ischemia (blood clots/ hemorrhage)

Augmented biological effects (from experiments)

- Hyp can cause cell death and stimulate the immune system (41°-45°C on tumor, normal cells unchanged)
- Inhibits the repair of radiation-induced DNA damage ⇒ increased cytotoxic effect of RT
- Improves blood flow ⇒ increases tissue oxygenation ⇒ cells more sensitive to RT
- Hyp-quickened apoptosis is thought to induce cell death by causing intracellular oxidative stress (deficient apoptosis can encourage carcinogenesis and tumor development)





Heat plus radiation: examples of clinical studies (I)

See also Liebl et al, Clin. Exp. Medicine 22, 519 (2022)

Table 1. Randomised trials on hyperthermia

Ref	Tumour site	Control	Experimental	Number of patients	Primary endpoint	Hyperthermia better (p<0·05)	Survival benefit
Local hyperthermia							
38	Head and neck (primary)	Radiotherapy	Radiotherapy and local hyperthermia	65	Response at 8 weeks	Yes	No
39	Melanoma (metastatic or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	68 (128 lesions)	Complete response (at 3 months)	Yes	No
40	Superficial (head and neck, breast, miscellaneous)	Radiotherapy	Radiotherapy and local hyperthermia	245	Initial response	possibly	No
41	Head and neck (N3 primary)	Radiotherapy	Radiotherapy and local hyperthermia (2–6 times)	44	Response (3 months)	Yes	Yes
42	Breast (advanced primary or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	307 (317 lesions)	Initial response	Yes	No
53	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	173 (240 lesions)	Best response	No	No
54	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	41 (44 lesions)	Initial response	No	No
55	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 2x local hyperthermia	Radiotherapy and 6x local hyperthermia	70 (179 lesions)	Initial response	No	No
Regional hyperthermia							
44	Cervix uteri (primary, stage III)	Radiotherapy	Radiotherapy and regional hyperthermia	40	Initial complete response	Yes	No
14	Primary or recurrent pelvic (cervix, rectum, bladder)	Radiotherapy	Radiotherapy and regional hyperthermia	361	Complete response rate, survival	Yes	Yes
Ongoing	Rectum (uT3/4)	Radiotherapy and chemotherapy	Radiotherapy, chemotherapy, and regional hyperthermia	>150	Disease-free survival		
Ongoing	Soft-tissue sarcoma (high risk)	Chemotherapy	Chemotherapy and regional hyperthermia	>150	Disease-free survival		

Heat plus radiation: examples of clinical studies (II)

Table 1. General trial characteristics.

	HIPEC N = 123	Regional N = 44	Local N = 45	WBH N = 15	Unknown N = 8	Total N = 235
Phase						
I	17	9	12	2	0	40
II	55	15	12	8	5	95
III	37	11	5	1	2	56
NA	14	9	16	4	1	44
Enrollment						
0–50	64	23	30	12	4	133
51–100	21	9	7	0	1	38
101–200	13	4	3	2	2	24
>200	24	8	5	1	0	38
X	1	0	0	0	1	2
Funder type						
Public	83	24	24	11	3	145
Hospital	24	10	7	1	2	44
Private	16	10	14	3	3	46
Status[a]						
Ongoing	31	16	13	4	1	65
Completed	58	20	20	2	0	100
Not completed	12	5	5	1	4	27
Unknown	22	3	7	8	3	43

Studies classified according to hyperthermia type, study phase, enrollment, funder type and status. When the phase was not provided by ClinicalTrials.gov, it is stated as not applicable (NA).
[a]Status is classified under ongoing: recruiting, not yet recruiting and suspended. Classified under not completed: withdrawn and terminated.

See also :

Liebl et al, Clin. Exp. Medicine 22, 519 (2022)

Tables taken from :

Peeters et al, Int,J, Hyp. 39, 896 (2022)

Table 2. Distribution of hyperthermia studies around the world and in Europe.

A	World	Phase 1	Phase II	Phase III	NA	Total
	North America	31	40	8	10	89
	Europe	6	29	25	17	77
	Asia	2	21	17	16	56
	Middle East	0	1	0	1	2
	South Africa	0	0	1	0	1
	South America	0	1	0	0	1
	Multicenter	1	2	5	1	9
	Total	40	94	56	45	235
B	Europe	Phase 1	Phase II	Phase III	NA	Total
	Germany	2	8	6	5	21
	UK	2	0	1	1	4
	France	0	3	3	1	7
	Italy	1	4	2	3	10
	The Netherlands	1	2	4	0	7
	Austria	0	1	1	0	2
	Switzerland	0	2	0	1	3
	Spain	0	1	4	0	5
	Portugal	0	0	0	1	1
	Sweden	0	1	1	1	3
	Norway	0	1	0	0	1
	Belgium	0	4	1	1	6
	Poland	0	2	1	0	3
	Greece	0	0	0	1	1
	Finland	0	0	0	1	1
	Unknown	0	0	1	0	1
	Multicenter Europe	1	0	4	1	6
	Total	7	29	29	17	82

Table 3. All phase III trials including (A) local and regional hyperthermia and (B) HIPEC.

A	Reference	ClinicalTrials.gov	Treatment	Cancer type	Nr. of patients per arm (control, exp. group)	Response	Control (%)	HT (%)
	Minnaar CA et al. [13]	NCT03332069	mEHT	Cervical cancer	100, 102	2-year OS DFS	43 14	53 36
	Issels RD et al. [29]	NCT00003052	CT, CTRTHT	Soft tissue sarcoma	169, 172	5-year OS 10-year OS	51 43	63 53
	Tan WS et al. [30]	NCT01094964	RITE	Bladder cancer	56, 48	DFS CR	24 30	53 47
	Chi MS et al. [31]	NCT01842048	RT, RTHT	Bone metastasis	29, 28	CR	7	38
	Ott OJ et al. [32]	NCT02369939	CTRT, CTRTHT	Squamous cell carcinoma	62, 50	5-year OS	75	96
	Zolciak-Siwinska A et al. [33]	NCT01474356	RT, RTHT	Cervical cancer	109, 96	DFS LC	67 84	60 88

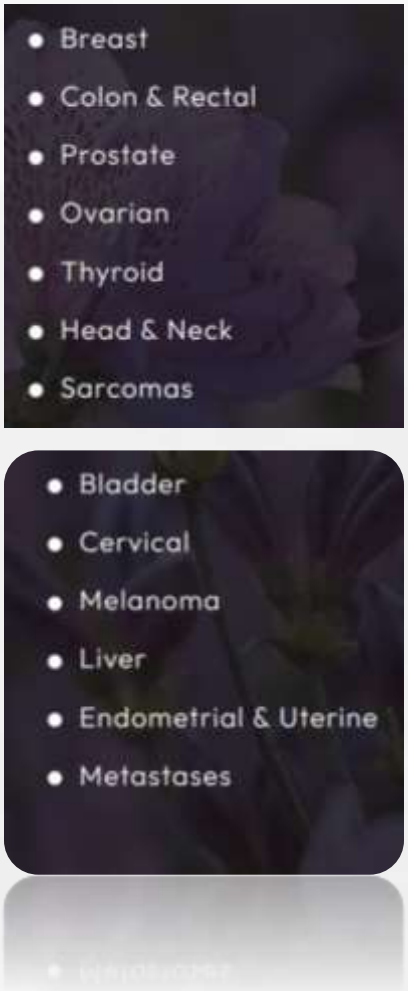
B	Reference	ClinicalTrials.gov	Treatment	Cancer type	Nr. of patients per arm (control, exp. group)	Response	Control	HT
	Lim MC et al. [34]	NCT01091636	HIPEC after primary or interval surgery	Ovarian cancer	92, 92	PFS OS	19 months 61 months	20 months 70 months
	Liu L et al. [35]	NCT02396498	HIPEC after surgery	Gastric cancer	57, 57	DFS	15 months	29 months
	Quénet F et al. [36]	NCT00769405	HIPEC after surgery	Colorectal cancer	133, 132	OS	41 months	42 months
	Goéré D et al. [37]	NCT01226394	HIPEC after surgery	Colorectal cancer with metastasis	75, 75	5-year OS	68%	72%
	Lei Z et al. [38]	NCT02356276	HIPEC after surgery	Ovarian cancer	159, 425	3-year OS Median ST	50% 34 months	60% 40 months
	Van Driel VW et al. [39]	NCT00426257	HIPEC after surgery	Ovarian cancer	123, 122	Median OS	34 months	46 months

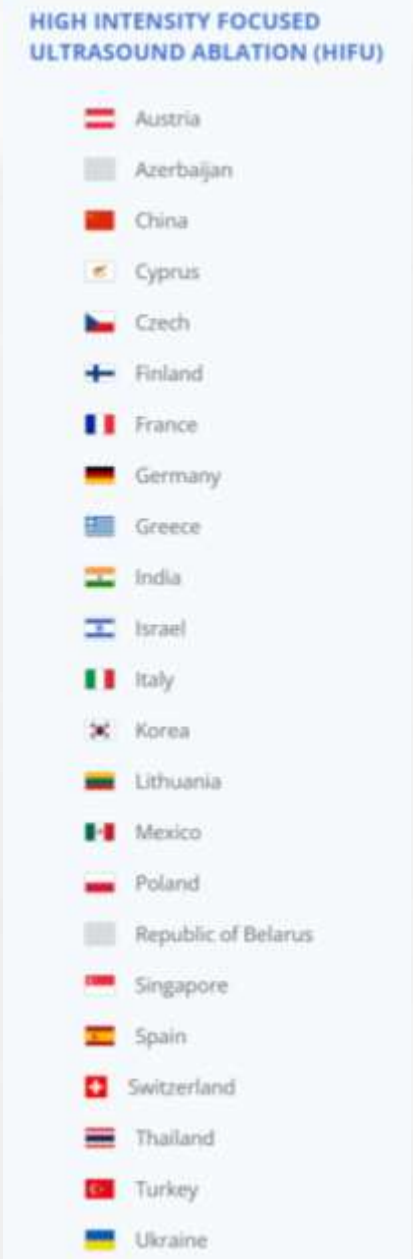
mEHT: modulated electro-hyperthermia; CT: chemotherapy; RT: radiotherapy; HT: hyperthermia; RITE: radiofrequency-induced thermo chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; OS: overall survival; DFS: disease free survival; CR: complete response; LC: local control; PFS: progression-free survival; ST: survival time

Highly-Focused Ultra Sounds technique

USA example : Hyperthermia Cancer Institute
2001 Santa Monica Blvd. Suite 1190W
Santa Monica, CA 90404
https://www.hcioncology.com/

- It delivers FDA-approved non-invasive hyperthermia therapy
- Hyperthermia utilizes HiFU heat to damage integrity/DNA structure of cancer cells
- Heat also increases blood flow and oxygenation, enabling higher concentrations of ChT / RT
- Hyperthermia also stimulates patient's immune system to recognize & fight cancer cells
- With Hyp, RT and ChT have a statistically higher chance of a complete response.





https://mediglobus.com/clinics/country-germany/specialities-high-intensity-focused-ultrasound-ablation-hifu/

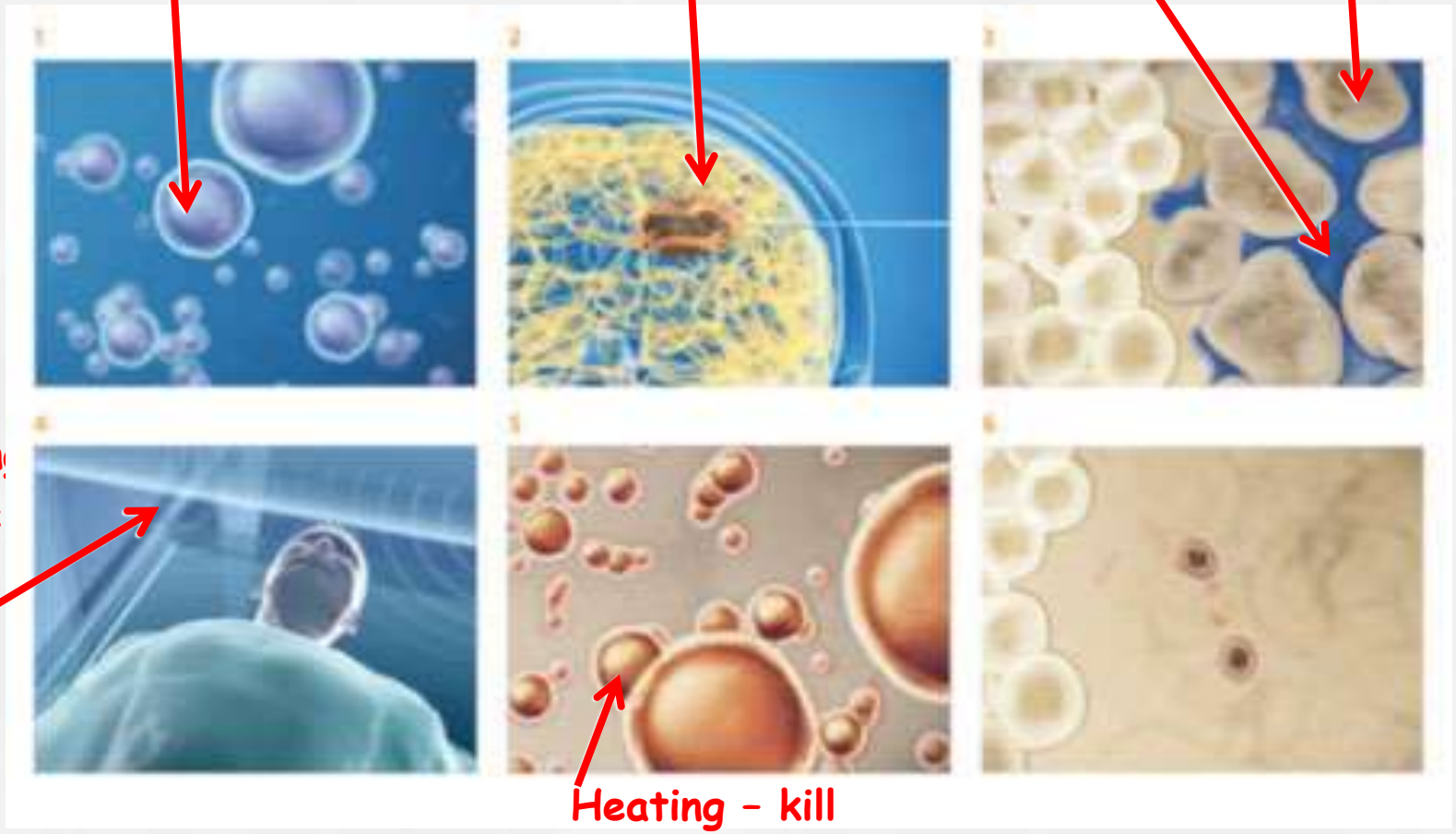
Magnetic Fluid Hyperthermia – Clinic (increased survival time up to 2 times)

MNPs coated
With amminosilane

Direct injection in
the brain tumour

Tumour cells

ferrofluid



Alternating
Magnetic
Field

Heating – kill
tumour cells

Combined therapies: hadrons and Hyp

Generally Hyp is applied together
with std radiotherapy (e.g. photons)
and/or chemotherapy

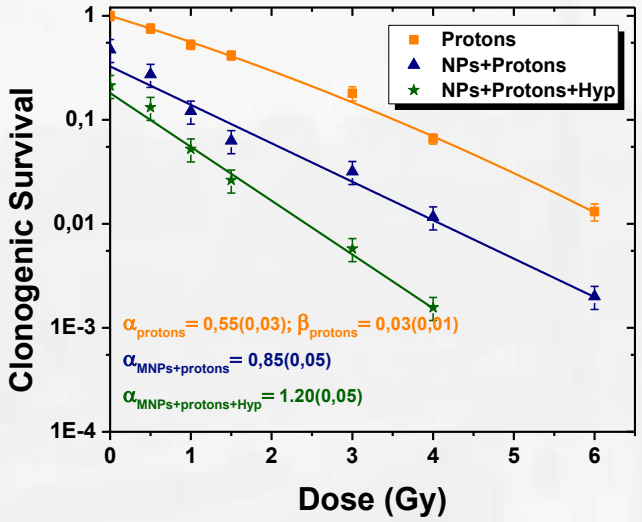
....

When the tumor is radioresistant: Hyp/MFH together with
proton (hadron) therapy (BNCT ??)

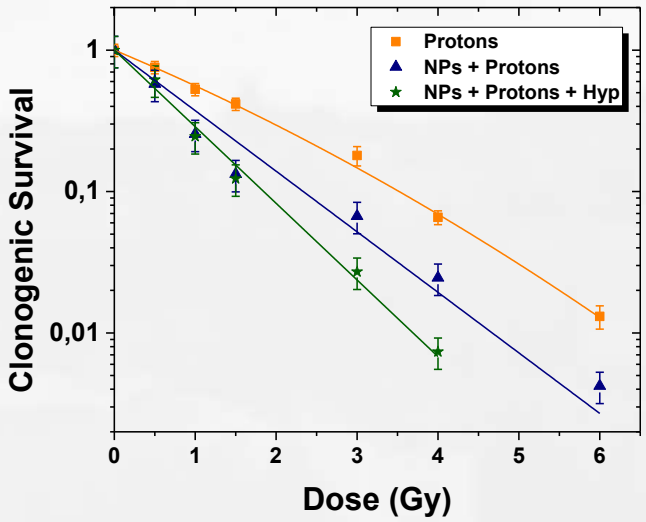
Proton therapy entered the hospitals as other alternative to RT

In vitro: HadronTherapy and (MFH) Hyp

3 independent experiments

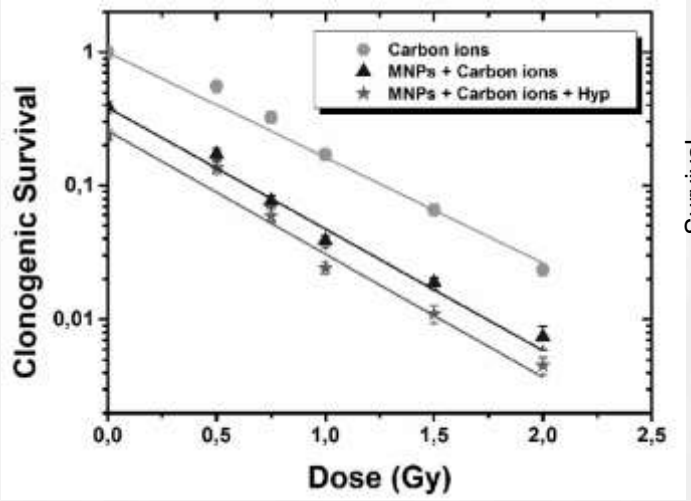


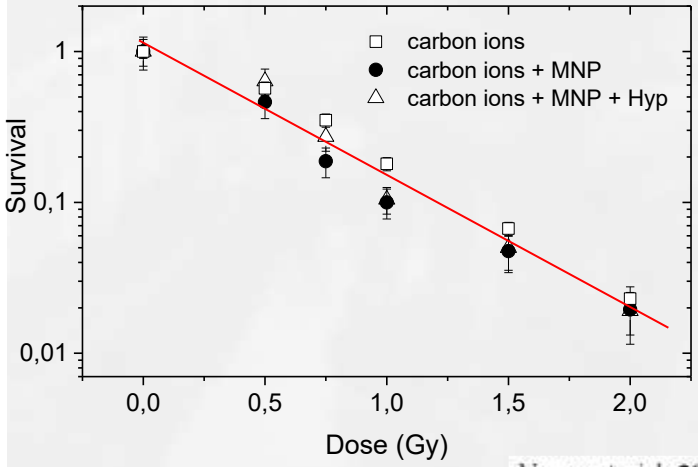
3 independent experiments



Irradiation with protons + (MFH)Hyp

<u>In-vitro experiments</u>
BxPc3 pancreatic tumor cells





Irradiation with carbon ions + (MFH)Hyp

Nanomaterials **2020**, *10*, 1919; doi:10.3390/nano10101919

Actual "main" recent collaborators

Dept. of Physics "A.Volta", Univ. of Pavia, INFN and INSTM, Pavia (Italy)
F. Brero, M. Porru, M. Mariani, M. Avolio, L. Bordonali, D. Cicolari, M. Corti, M. Cobianchi, T. Orlando
Dept. of Physics, Università degli studi di Milano , INFN and INSTM, Milano (Italy)
P. Arosio, F. Orsini, M. Basini, D. Bettega, P. Calzolari, S. Gallo, F. Groppi, C. Lenardi , S. Locarno, S. Manenti, I. Veronese
Dept. of Chemistry and INSTM, Univ. of, Sesto Fiorentino (FI) (Italy)
C. Sangregorio (CNR), M. Albino, C. Innocenti, A. Laurenzana, A. Caneschi, F. Pineider, E. Fantechi, A. Guerrini, D. Gatteschi
Dept. of Physics, Università degli studi di Bologna, Bologna (Italy)
S. Sanna
CNR –ISM, Roma (Italy)
D. Peddis
ICMM/CSIC, Madrid (Spain)
M. Del Puerto Morales, J.G. Ovejero (also INMA-Zaragoza)
Mons University, Mons (Belgium)
Y. Gossuin, Q.L. Vuong
Nantes University, Nantes (France)
E. Ishow, L. Lartigue
University of Zaragoza, Zaragoza (Spain)
A. Millan, F. Palacio, R. Pinol
CNR-IOM , Trieste (Italy)
V. Bonanni (Elettra, Trieste), G. Rossi (UNIMI), P. Torelli
Dept. of Chemistry, Università degli studi di Roma III, and INFN, Roma (Italy)
A. Antoccia, F. Berardinelli
FORTH-Greece
A. Lappas

COST-RADIOMAG, COST-EURELAX, COST-MyWave, INSTM-RL-Motorsport , UNIMI-Young Researchers
INFN-Hadrocombi/Hadromag/Prothyp/Mather3D

Some recent bibliography (not exhaustive !!)

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Thank you !