CORSO SOCIETÀ ITALIANA DI OSTEONCOLOGIA - ISO

23 APRILE 2024 ROMA ISTITUTO DI STORIA DELLA MEDICINA

QUALI STRATEGIE TERAPEUTICHE E QUALI NOVITÀ NELLA GESTIONE DELLE METASTASI OSSEE

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«L’ipertermia nel controllo del dolore oncologico limiti e applicazioni»

IPERTERMIA ONCOLOGICA

Definizione:

- L’ipertermia è una modalità terapeutica che prevede la somministrazione di calore il più possibile selettiva a un tessuto tumorale in un intervallo compreso tra 39,5 e 43°C per un periodo sufficientemente lungo.

- La moderna ipertermia oncologica nasce con la Consensus Conference di Osaka nel 2004

Definition Hypertermia

- Selective heating of tumor tissue
- Tumor target temperature: 39.5-43 °C
- Therapeutic time: 60 min
- Exclusively in combination with RT and/or CT

IPERTERMIA

EFFETTO SINERGICO DELL'IPERTERMIA

- Oggi conosciamo la perfetta sinergia con le terapie antitumorali comunemente usate:

Radioterapia – Chemioterapia - Immunoterapia

IPERTERMIA
innovazione tecnologica

- Sino a pochi anni fa non era possibile aumentare la temperatura del paziente senza creare rischi.

- Non si potevano raggiungere tumori profondi.

- Oggi, con le apparecchiature più avanzate e le nuove conoscenze è possibile raggiungere un tumore profondo senza determinare effetti collaterali importanti

IPERTERMIA
innovazione tecnologica

Principali modalità di somministrazione di ipertermia attraverso campi elettromagnetici

1. **Ultrasuoni**, onde meccaniche con frequenze comprese tra 0.3 e 3 MHz; o ultrasuoni focalizzati (HIFU)
2. **Microonde**, radiazioni elettromagnetiche di frequenza compresa tra 300 e 2450 MHz
3. **Radiofrequenze**, radiazioni elettromagnetiche di frequenza inferiore ai 300 MHz

IPERTERMIA ONCOLOGICA

NELLA IPERTERMIA ONCOLOGICA PROFONDA VENGONO USATE LE RADIOFREQUENZE

1. Ultrasuoni permettono di focalizzare l'energia in profondità ma subiscono il fenomeno della riflessione.

2. Microonde la penetrazione è di pochi centimetri

3. Radiofrequenze (13.56 MHz) si raggiungono profondità che superano i 20 centimetri

IPERTERMIA: principi fisici di base

IPERTERMIA ONCOLOGICA PROFONDA:

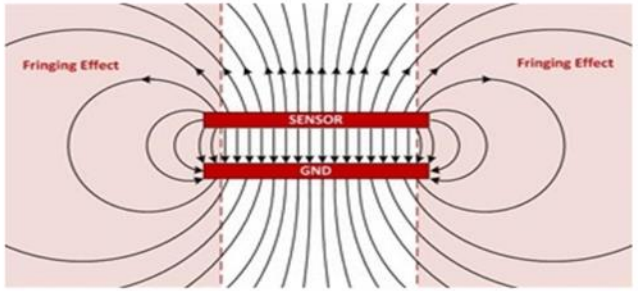
- apparecchiature di tipo CAPACITIVO
- apparecchiature di tipo RADIATIVO

Che si distinguono per la diversa modalità di distribuzione dei campi elettromagnetici in profondità

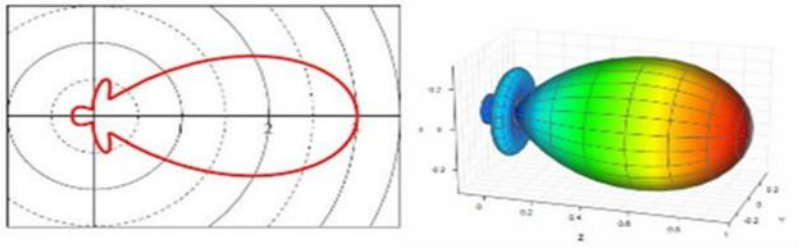
IPERTERMIA: principi fisici di base

Ipertermia profonda: possibili approcci

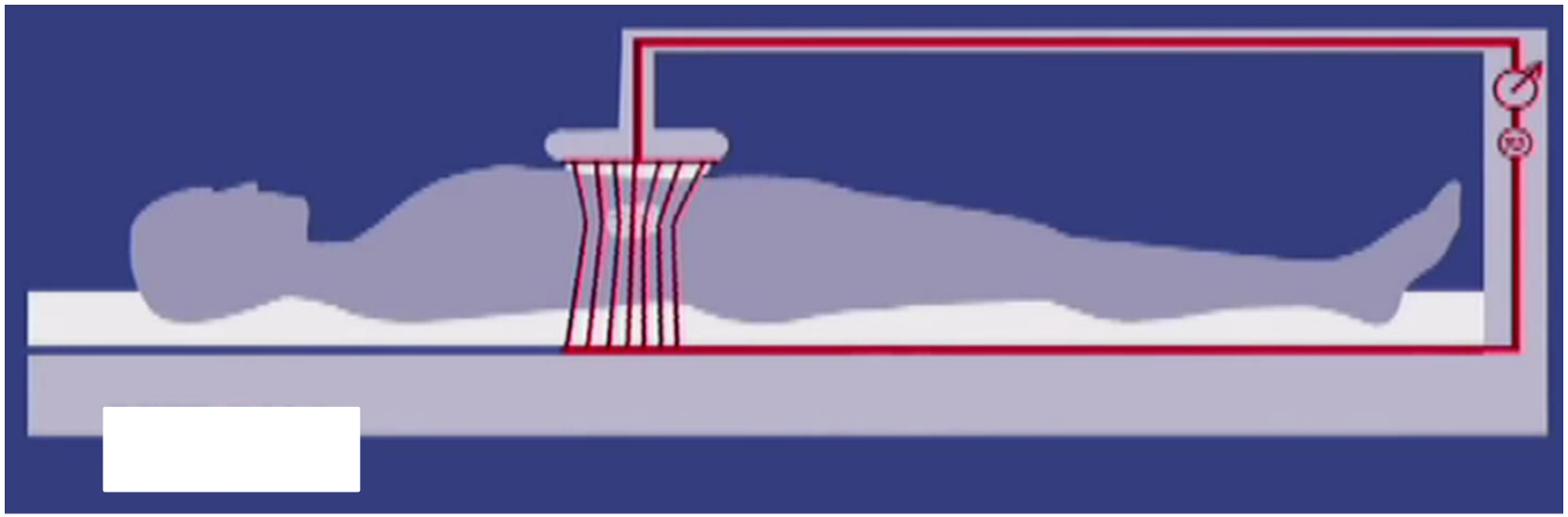
Sistemi capacitivi



Sistemi radiativi



IPERTERMIA ONCOLOGICA PROFONDA

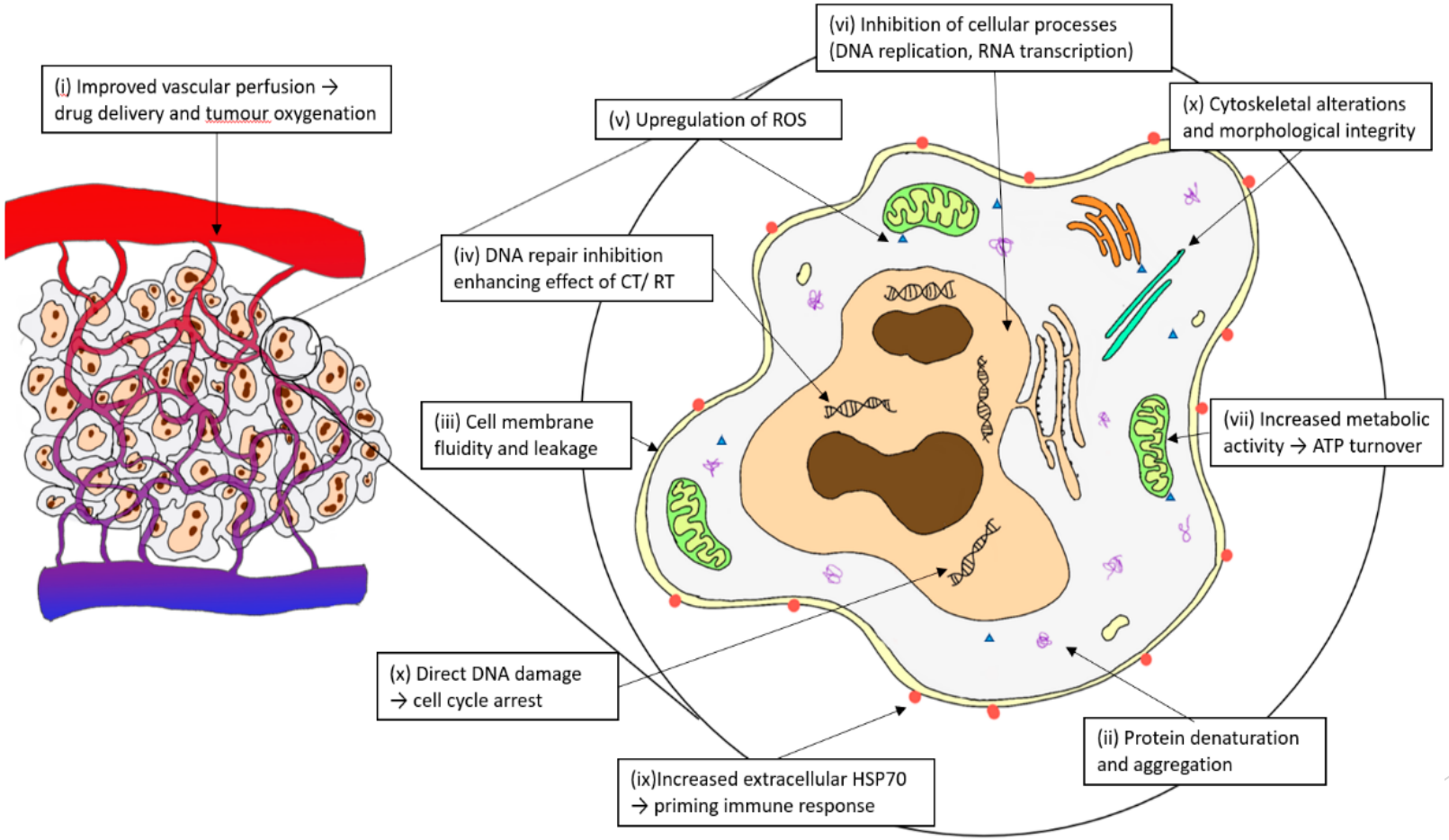


HYPERTERMIA AS RADIO-SENSITIZER

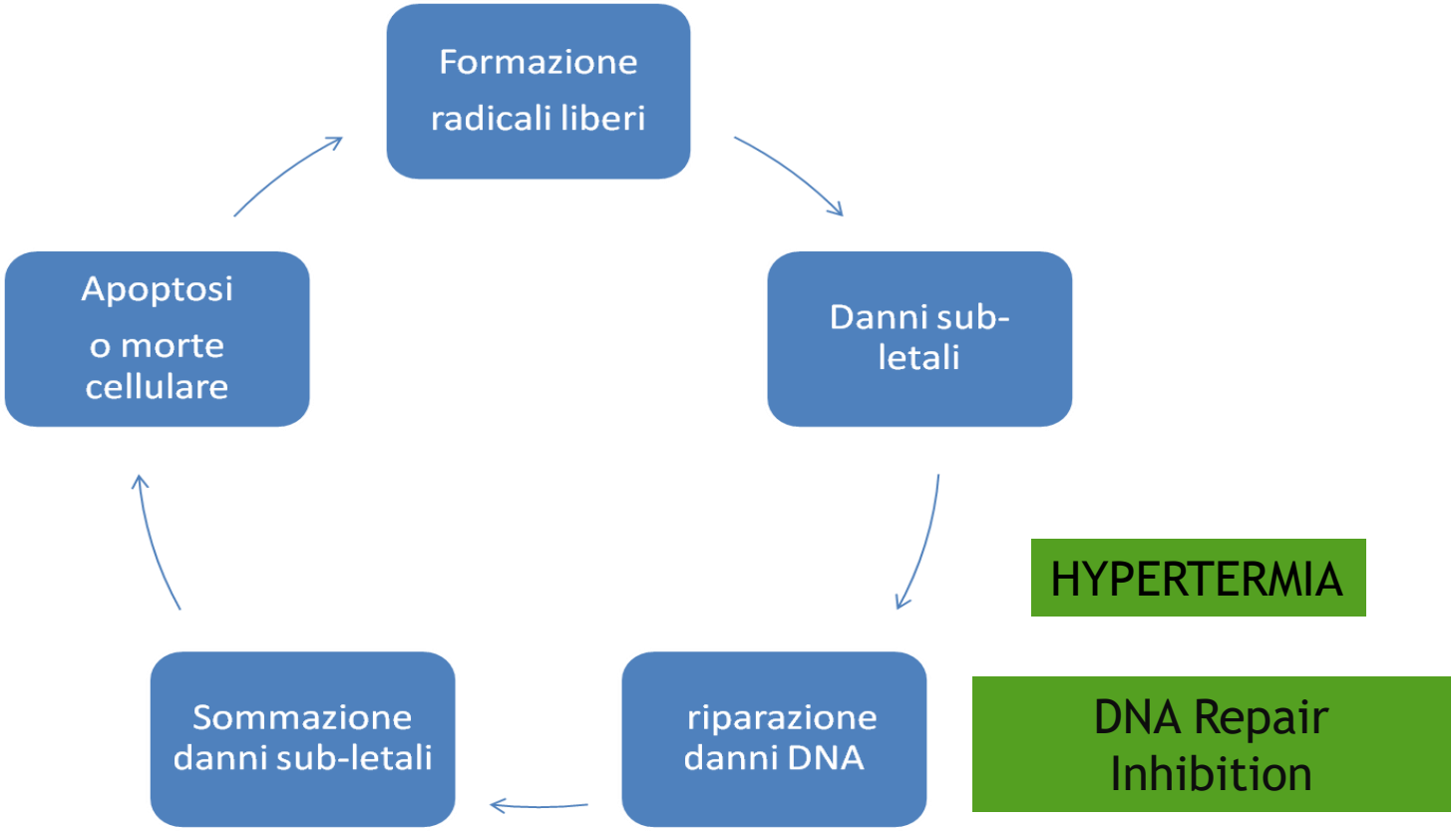
«Mild Hypertermia» with temperature between 41-43° works as a thermal sensitizer and **enhance** Radiation damage by:

- Inhibition of radiation induced DNA damage repair
- Sensitization of the «S» phase cells
- Oxygenation of hypoxic cells due to increased blood perfusion of tha heated tissue
- Immune stimulation

HYPERTERMIA AS RADIO-SENSITIZER



HYPERTERMIA AS RADIO-SENSITIZER



HYPERTERMIA

DNA Repair Inhibition

HYPERTERMIA AS RADIO-SENSITIZER

Schematic overview of the effect of Hyperthermia on DNA repair factors

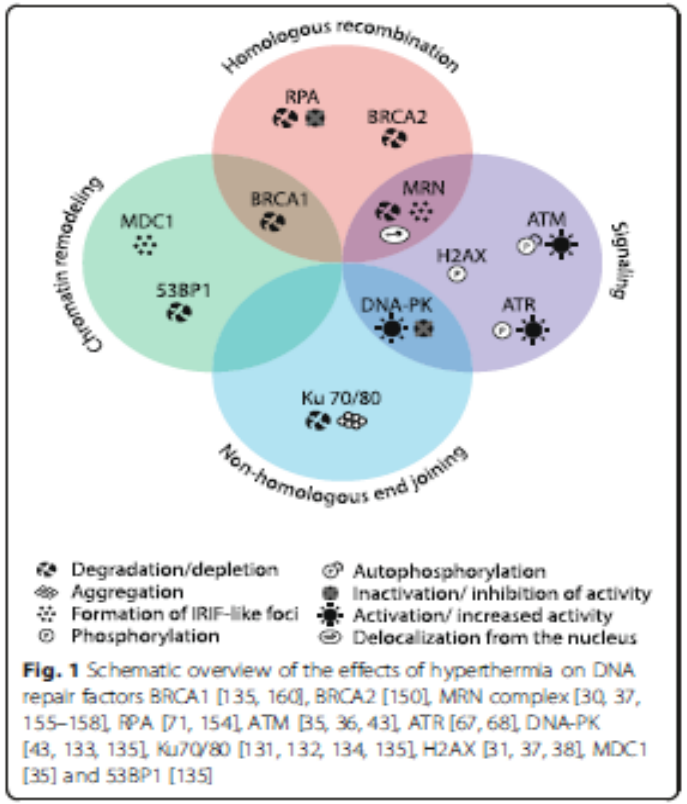


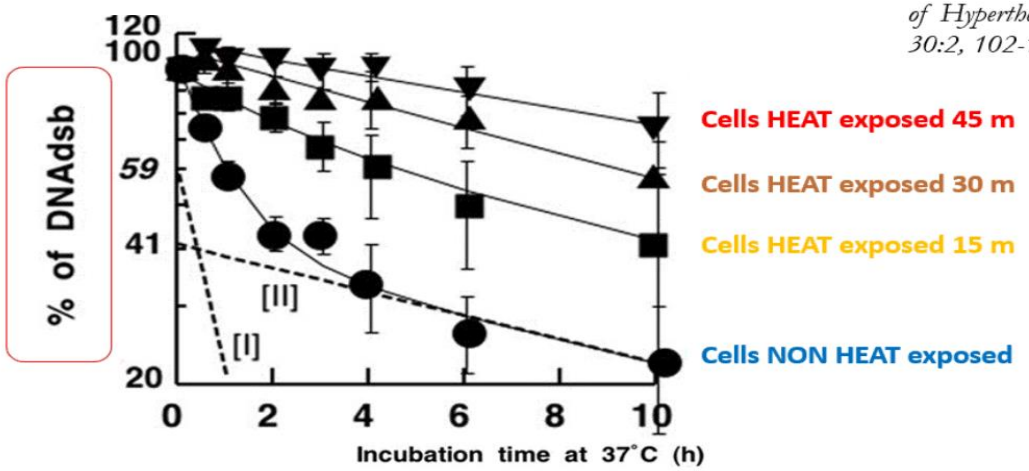
Fig. 1 Schematic overview of the effects of hyperthermia on DNA repair factors BRCA1 [135, 160], BRCA2 [150], MRN complex [30, 37, 155–158], RPA [71, 154], ATM [35, 36, 43], ATR [67, 68], DNA-PK [43, 133, 135], Ku70/80 [131, 132, 134, 135], H2AX [31, 37, 38], MDC1 [35] and 53BP1 [135]

Oei et al. Radiation Oncology (2015), 10:165

HYPERTERMIA AS RADIO-SENSITIZER

Hypethermia inhibits mechanisms of DNA repair

Makoto Ihara, et al. International Journal of Hyperthermia, 30:2, 102-109,2014

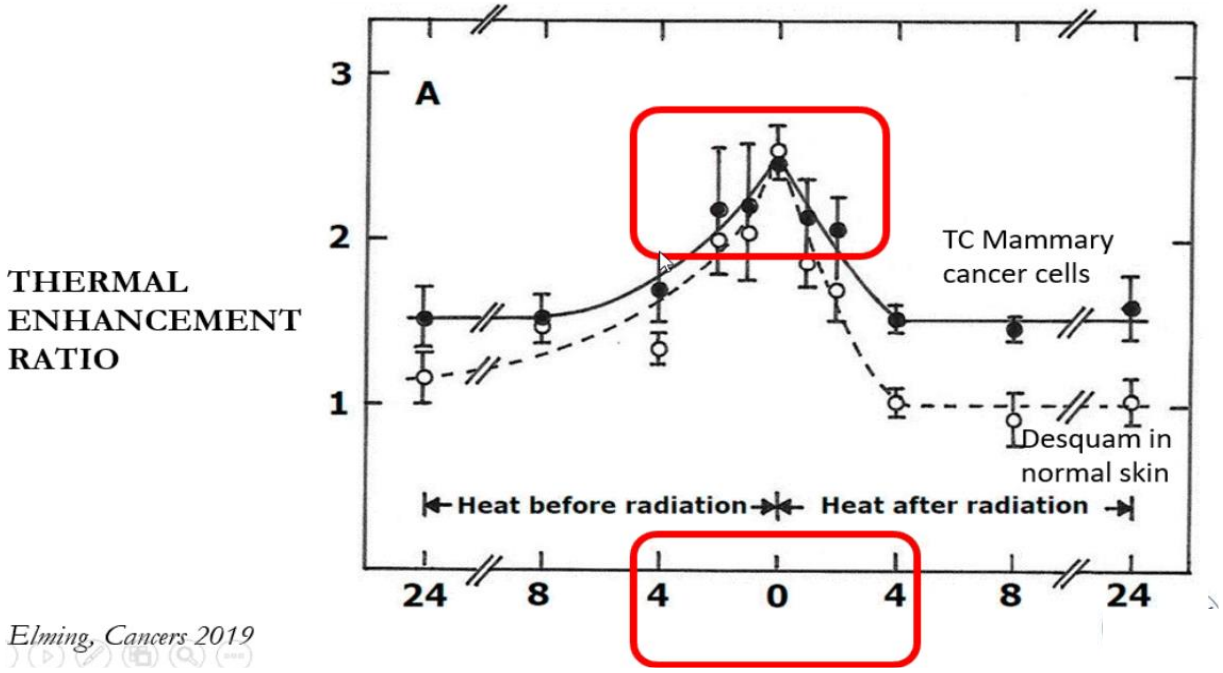


HYPERTERMIA AS RADIO-SENSITIZER

TIMING IS CRUCIAL:

Increasing the interval between ionizing radiation and heating will clearly allow for more repair to occur before the heat inhibits further repair, leading to less sensitization

HYPERTERMIA AS RADIO-SENSITIZER

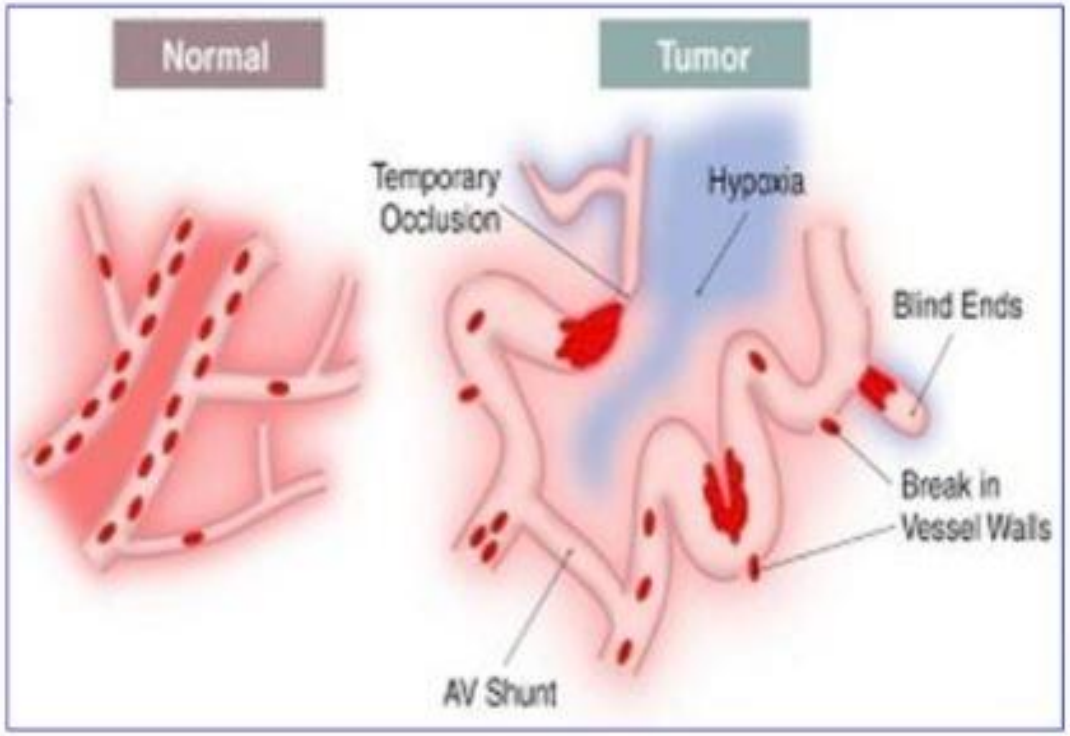


Elming, Cancers 2019

HYPERTERMIA AS RADIO-SENSITIZER

Physiological mechanism of radiosensitization by Hyperthermia

Mild Hyperthermia up to 42°C will **increase blood flow** and thereby decreasing hypoxia

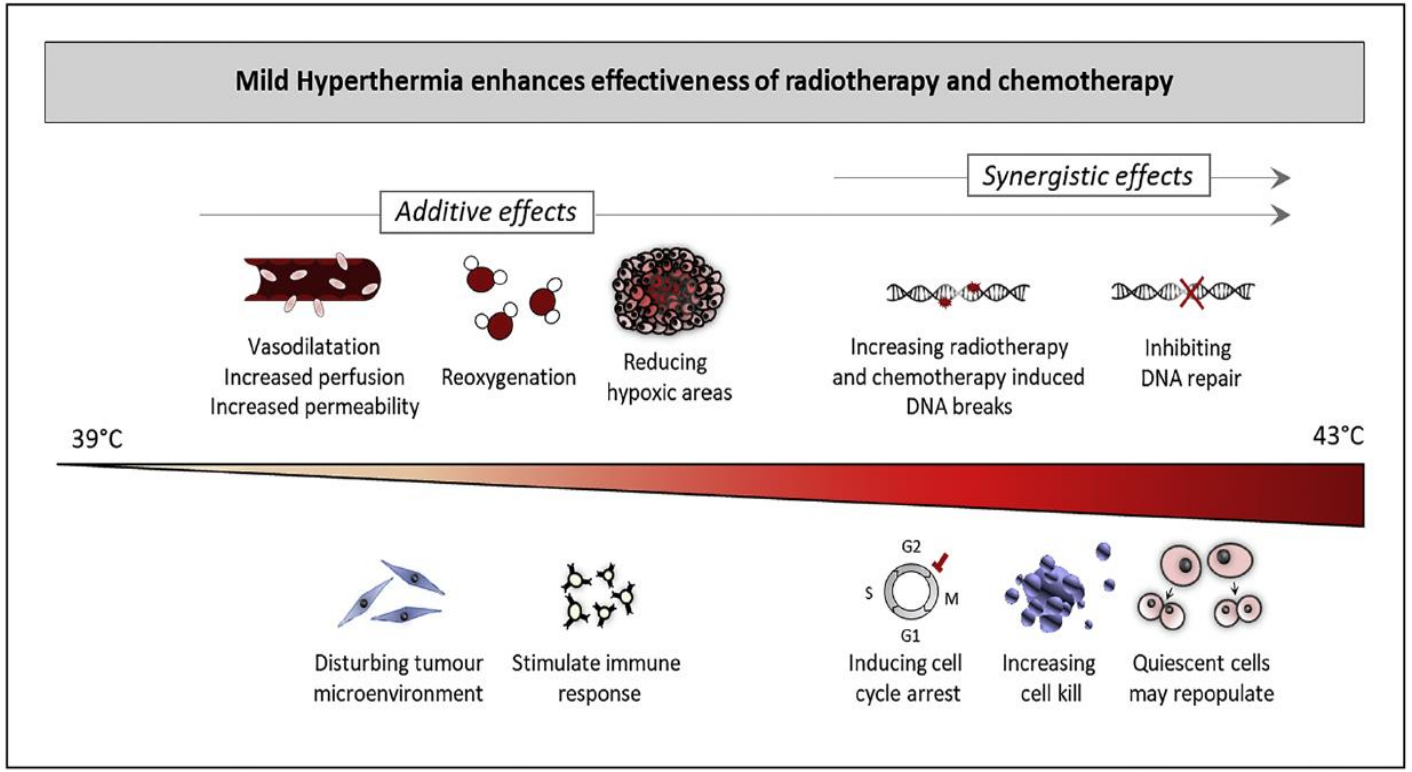


HYPERTERMIA AS RADIO-SENSITIZER

IMMUNE STIMULATION

- Increases expression of **immuno-genic surface receptors** such as MICA an MHC-I enhancing effectiveness and function of natural killer (NK) cel and of CD8+ cells
- The expression of **heat shock proteins** (HSPs) such as HSP70 is increase After binding intracellular proteins, HSPs get secreted stimulating th activity of NK cell- and antigen-presenting dendritic cells
- Immune cell trafficking is enhanced by increased perfusion and **permeability**. Following elevated intratumoral IL-6 signaling, it may further be facilitated by increased cell **adhesion molecule** expression such as ICAM-I

HYPERTERMIA AS RADIO-SENSITIZER



STUDIO PROSPETTICO RANDOMIZZATO E CONTROLLATO DI FASE III

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial

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Chi MS, et Al;

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial.

Int J Radiat Oncol Biol Phys.

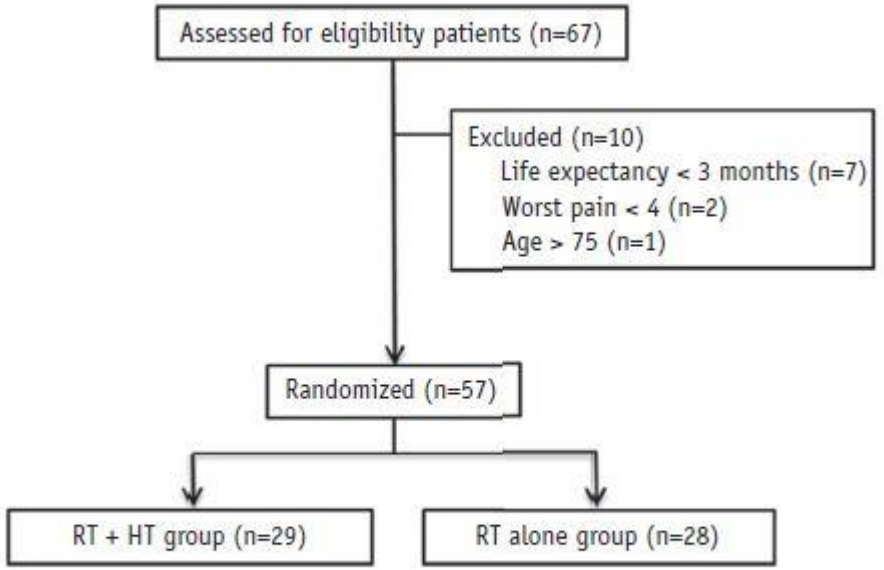

Fig. 1. Patient CONSORT flow diagram. *Abbreviations:* HT = hyperthermia; RT = radiation therapy.

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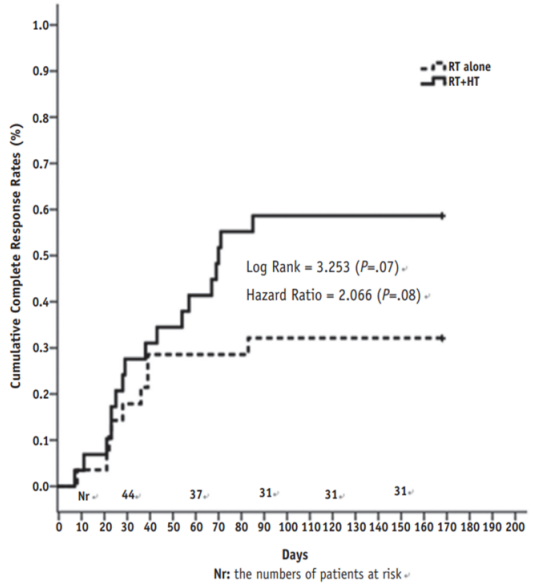

Fig. 2. Cumulative complete response rates in radiation therapy plus hyperthermia (RT + HT) and radiation therapy alone (RT-alone) group.

Chi MS,et Al:

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial.

Int J Radiat Oncol Biol

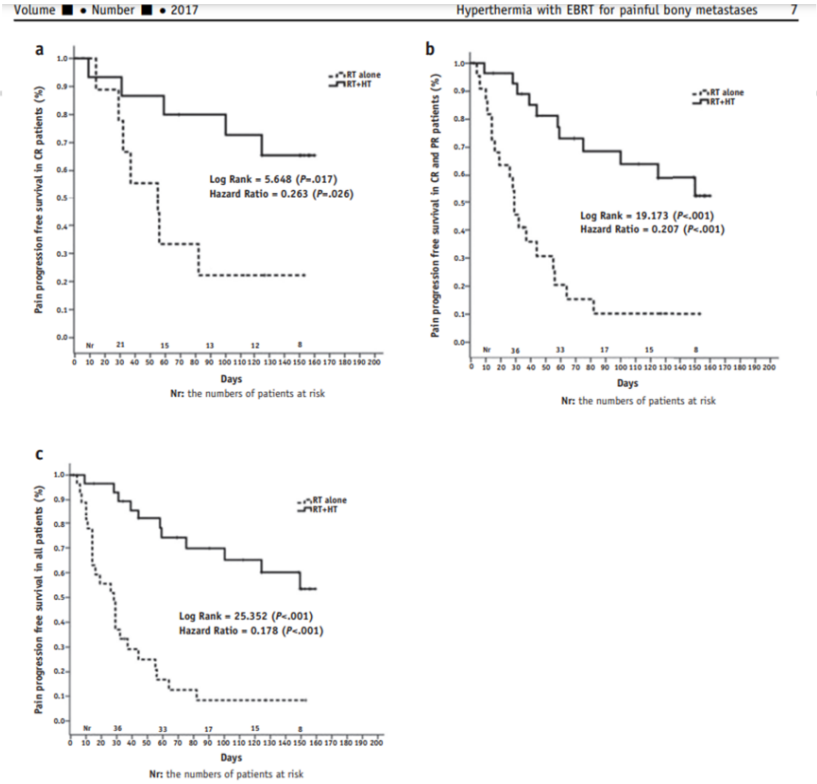

Fig. 3. Time to pain progression. (a) Time to pain progression in patients with complete response (CR). (b) Time to pain progression in patients with complete response (CR) and partial response (PR). (c) Time to pain progression in all patients. *Abbreviations:* HT = hyperthermia; RT = radiation therapy.

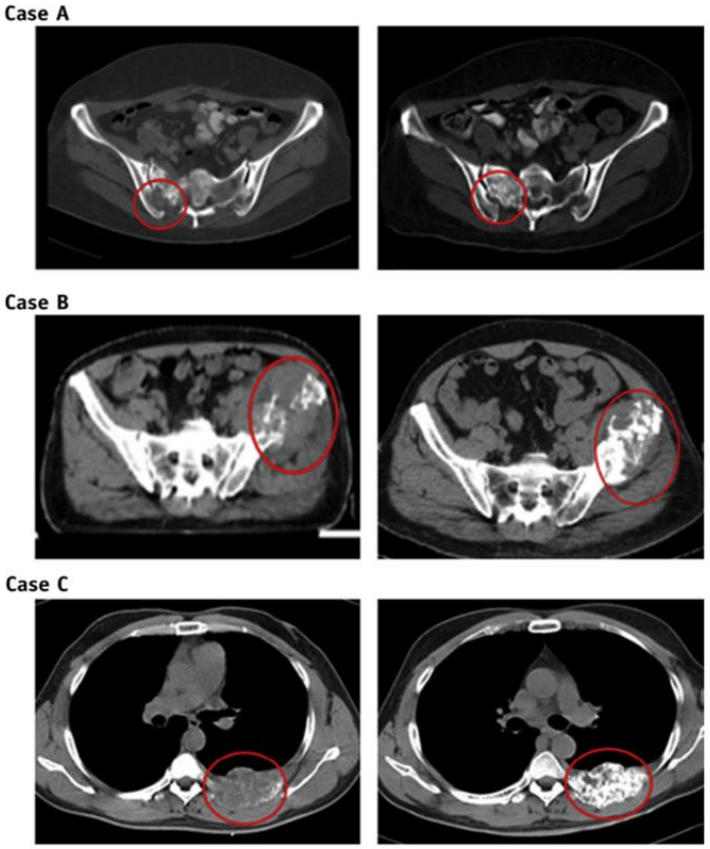

Fig. 4. Three cases of bone ossification of the osteolytic lesions after radiation therapy plus hyperthermia. Images presented were established within a 2-month period after treatment.

CONCLUDENDO…

Editorial

Radiotherapy plus hyperthermia shows effectiveness in painful bony metastases—indicated only for selected patients with extended live expectancy and radiotherapy resistant tumor!

Gerard Cornelis van Rhoon, Jeannette Maria Leonora van Holthe

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

- E’ realistico aggiungere l’ipertermia alla moderna RT, dove la preferenza crescente è quella di trattare i pz con dolore da meta ossee, con una singola frazione di 8 Gy?

- LINEE GUIDA ASTRO: **<u>medesima efficacia sul dolore</u>**
- 30 Gy in10 frazioni
- 24 Gy in 6 frazioni
- 20 Gy in 5 frazioni
- 8 Gy in unica frazione

Pazienti selezionati

- L’aggiunta della ipertermia alla RT a frazione singola potrebbe essere presa in considerazione nel gruppo selezionato di pz con buone condizioni e una aspettativa di vita prolungata, ma dove la sola RT potrebbe non essere efficace come nei tumori di grosse dimensioni o dopo precedenti trattamenti radioterapici

GRAZIE PER L'ATTENZIONE!!!