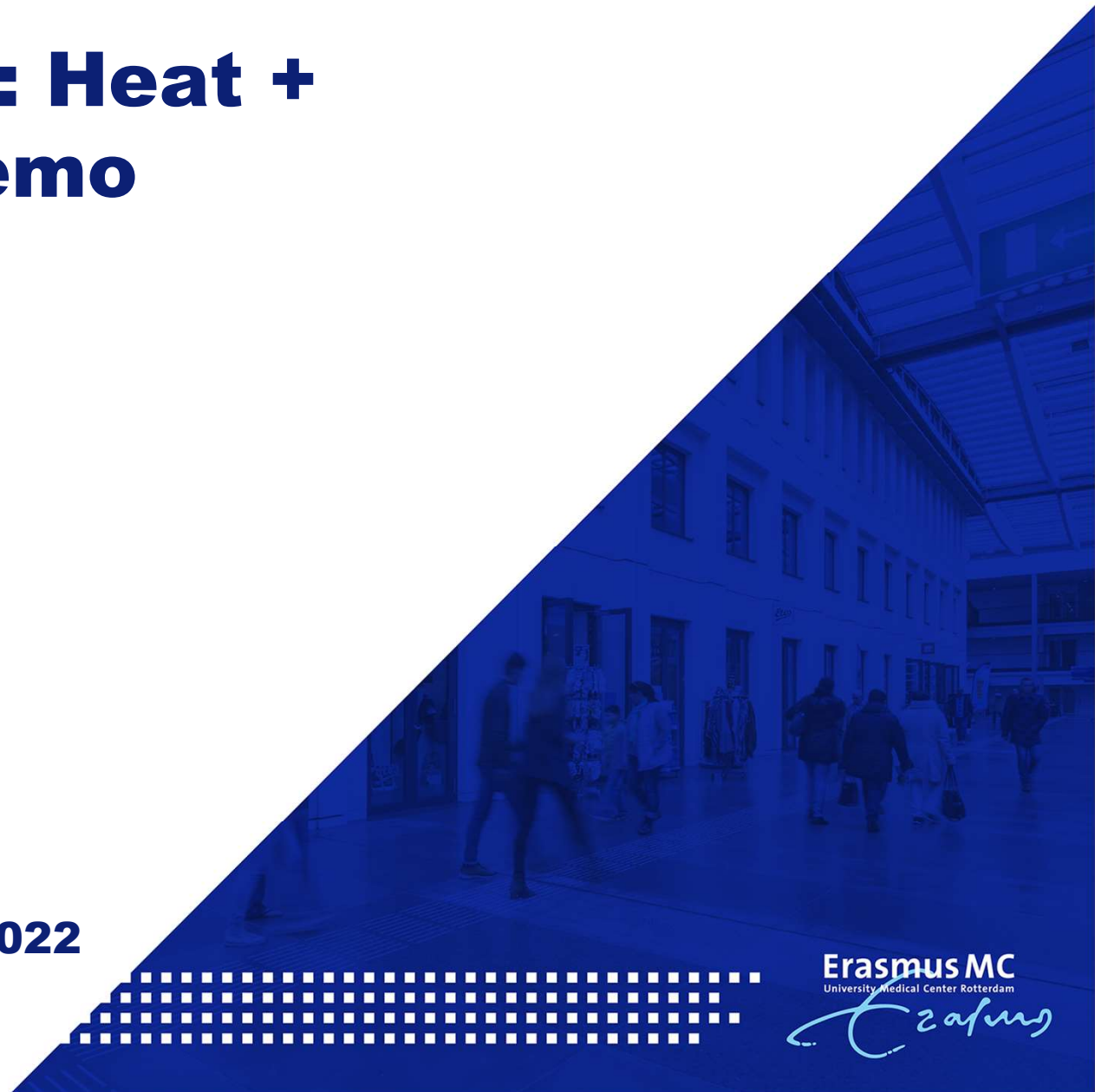


# **Synergistic effects: Heat + radiotherapy /+ chemo**

**Gerard C van Rhoon**  
Department of Radiotherapy

**ESHO school, September 13, 2022**  
**Gothenburg, Sweden**



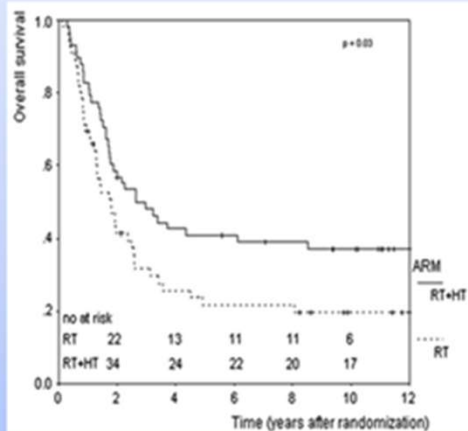
**Erasmus MC**  
University Medical Center Rotterdam



# Combining RT or CT with HT is effective

## Radiotherapy

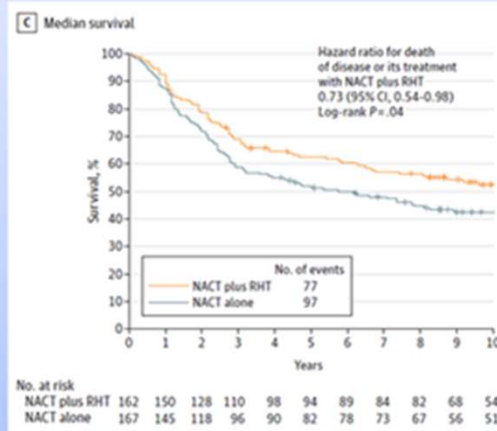
vd Zee et al. Franckena et al.  
Dutch Deep Hyperthermia Trial  
RT±HT in LACC: long term follow-up



THE LANCET Oncology 2000  
Radiation Oncology 2008  
Official Journal of the American Society for Radiation Oncology ASTRO

## Chemotherapy

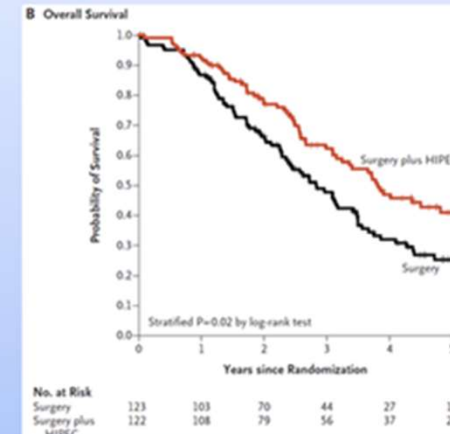
Issels et al. NAC+RHT: Long-term Outcomes Localized High-Risk Soft Tissue Sarcoma



JAMA Oncology 2018

## Chemotherapy

Van Driel et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

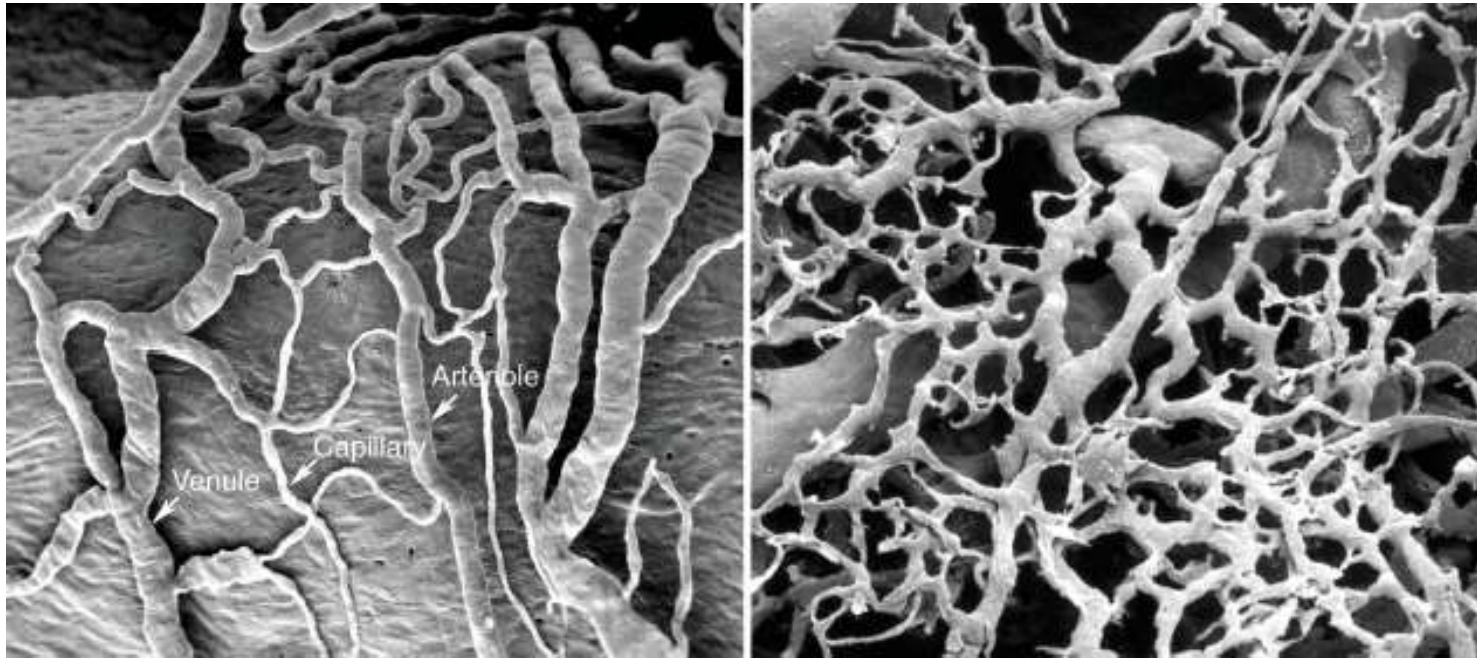


The NEW ENGLAND JOURNAL of MEDICINE 2018

# Levels of interaction hyperthermia with radiotherapy or chemotherapy

1. **Independent:** hyperthermia and RT/CT appear to act by independent mechanisms.
2. **Additive:** hyperthermia results in additional damage. With increasing temperature, the effectiveness of the cytotoxic mechanism is enhanced.
3. **Synergistic:** thermal sensitization to known effects occur with increasing temperature.

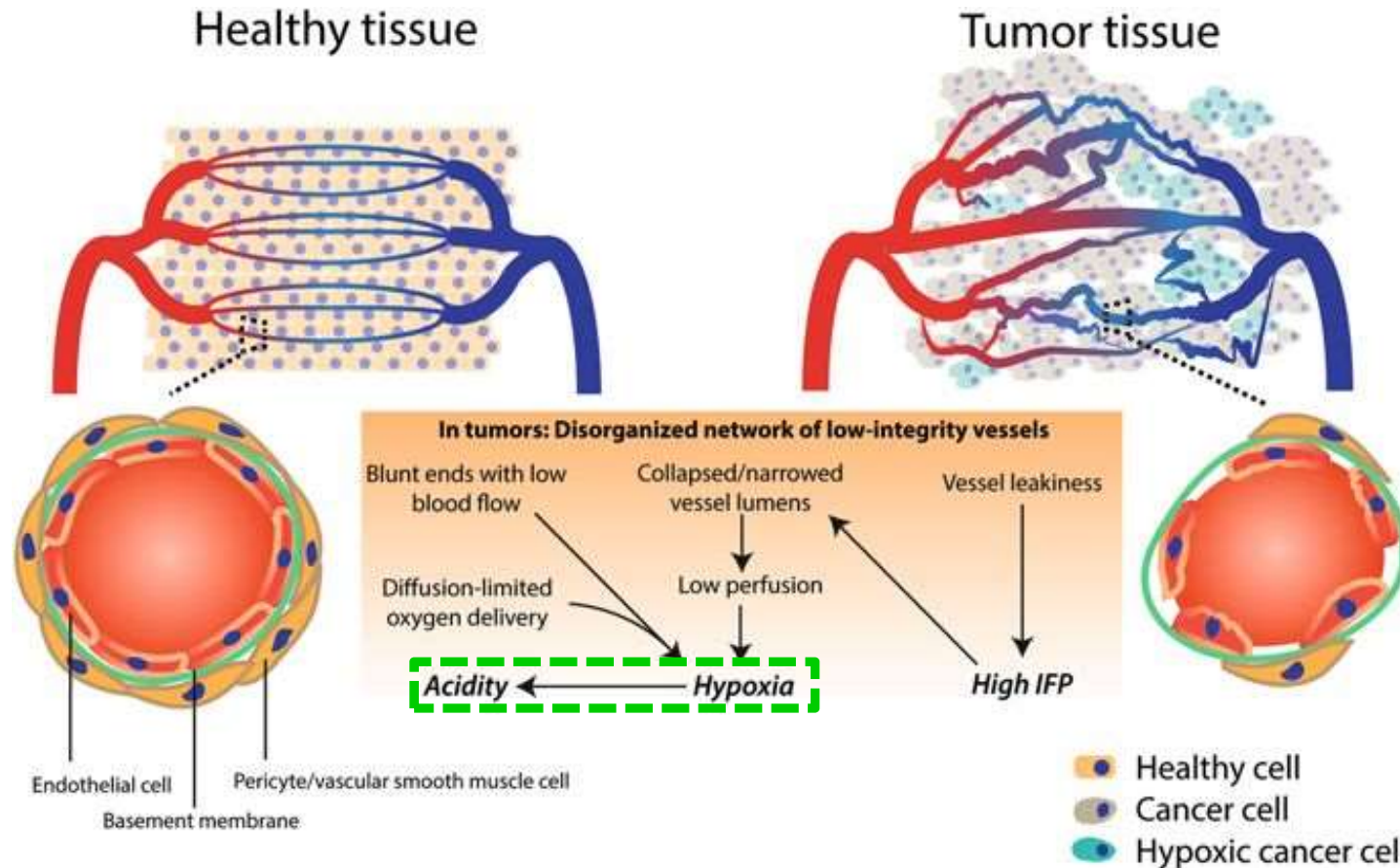
# Vasculature normal and malignant tissues.



*Normal tissue*

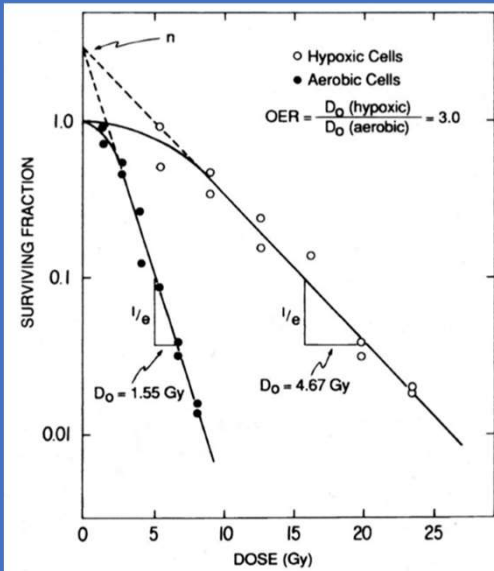
*Tumor tissue*

# Vasculature of normal and malignant tissues.

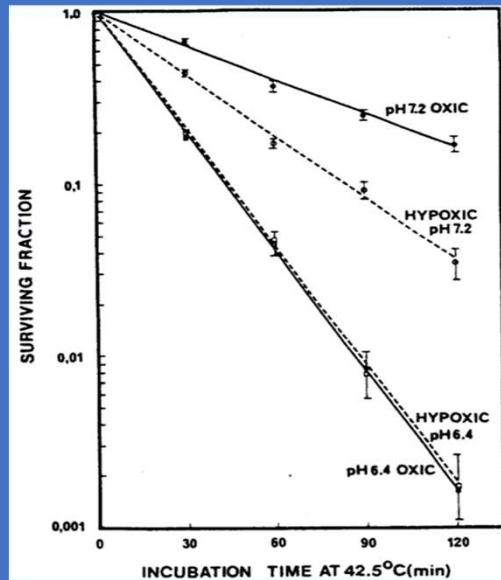


Ref.: Schaaf et al. Cell Death and Disease (2018)

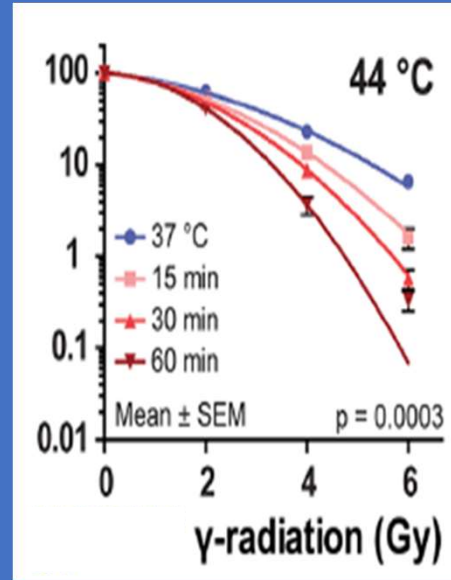
# Vasculature of normal and malignant tissues + RT sensitivity



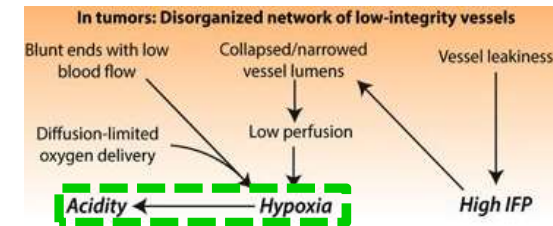
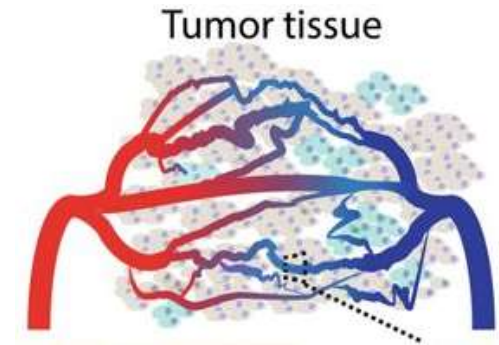
Rockwell et al, Curr Mol Med. 2009



Overgaard & Bichel, Radiol 1977

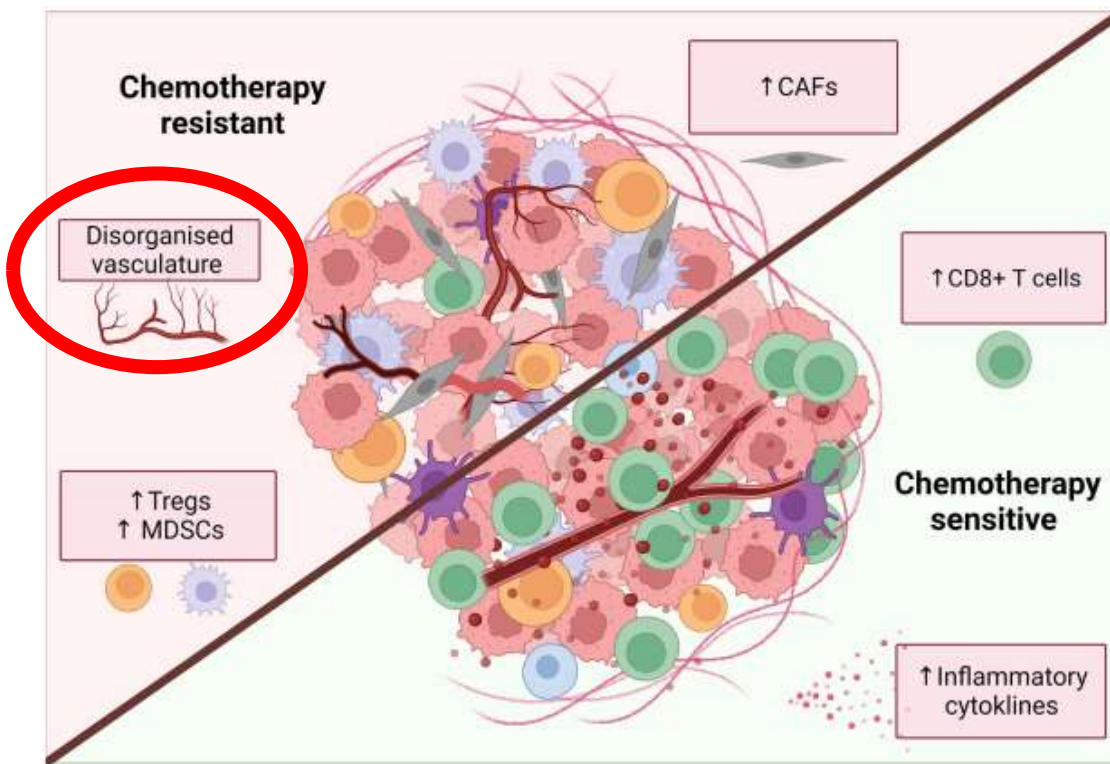


van den Tempel et al, Oncotarget 2017



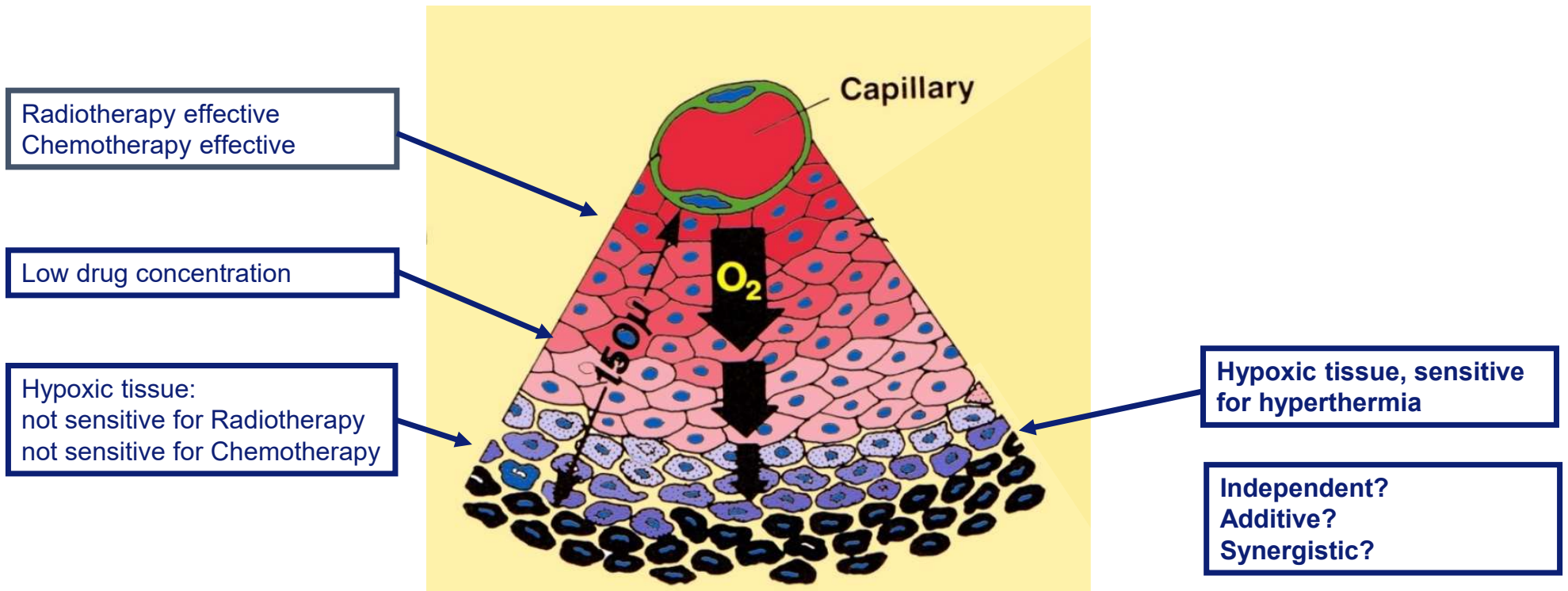
Ref.: Schaaf et al. Cell Death and Disease (2018)

# Vasculature of normal and malignant tissues + CT sensitivity



*TME - Tumor microenvironment*  
*CAF - Cancer associated fibroblasts*  
*Tregs - Regulatory T Cells*  
*MDSCs - Myeloid-derived suppressor cells*  
*CD8+ T Cells - cytotoxic T lymphocytes*

# Impact different vasculature of normal and malignant tissues.



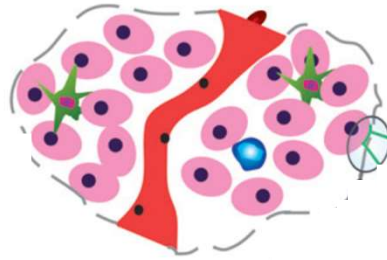
J.M. Brown Cancer research 1998

ErasmusMC



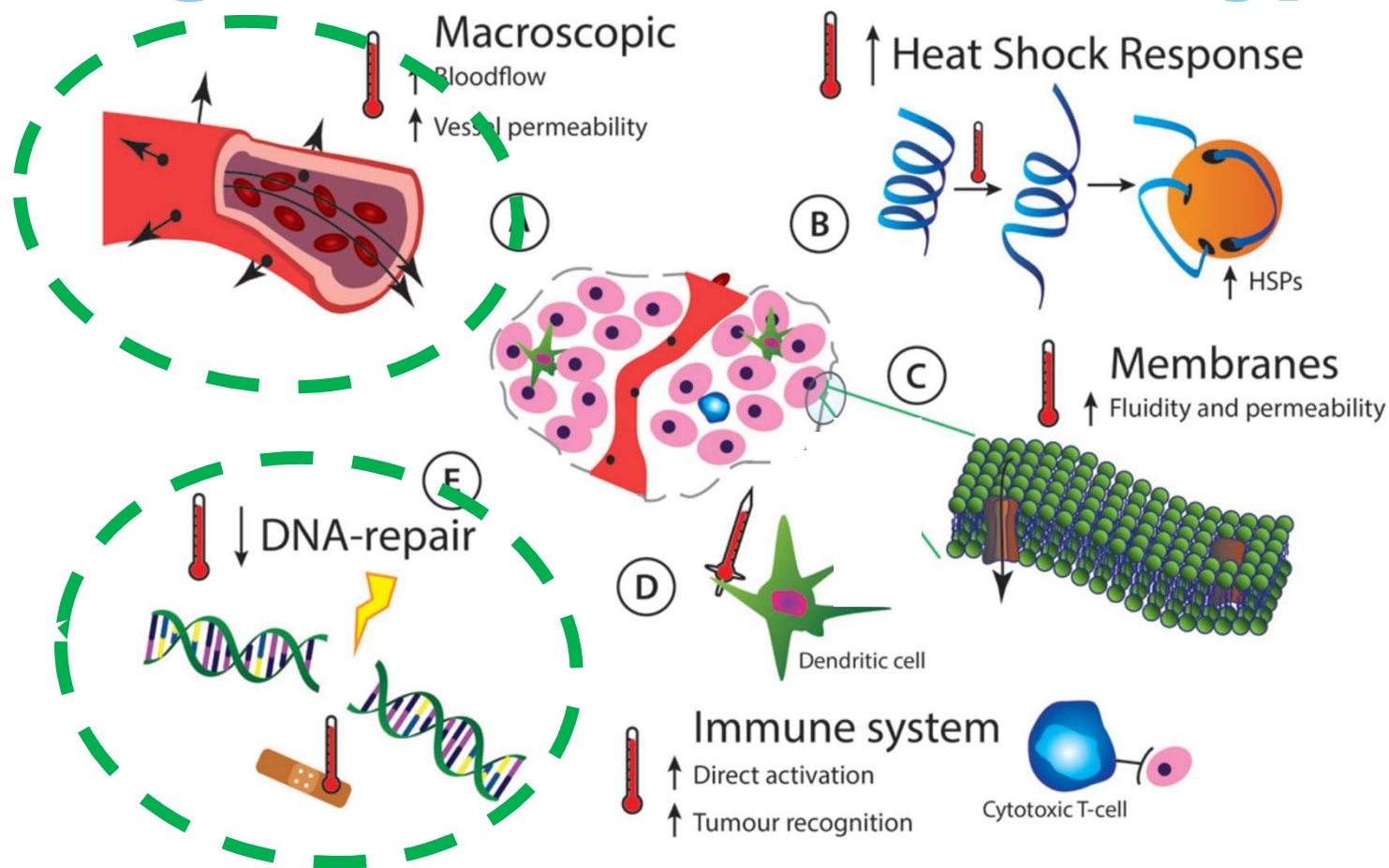


# Biological mechanisms of hyperthermia



Jen Tempel et al.  
Hyperthermia 2016

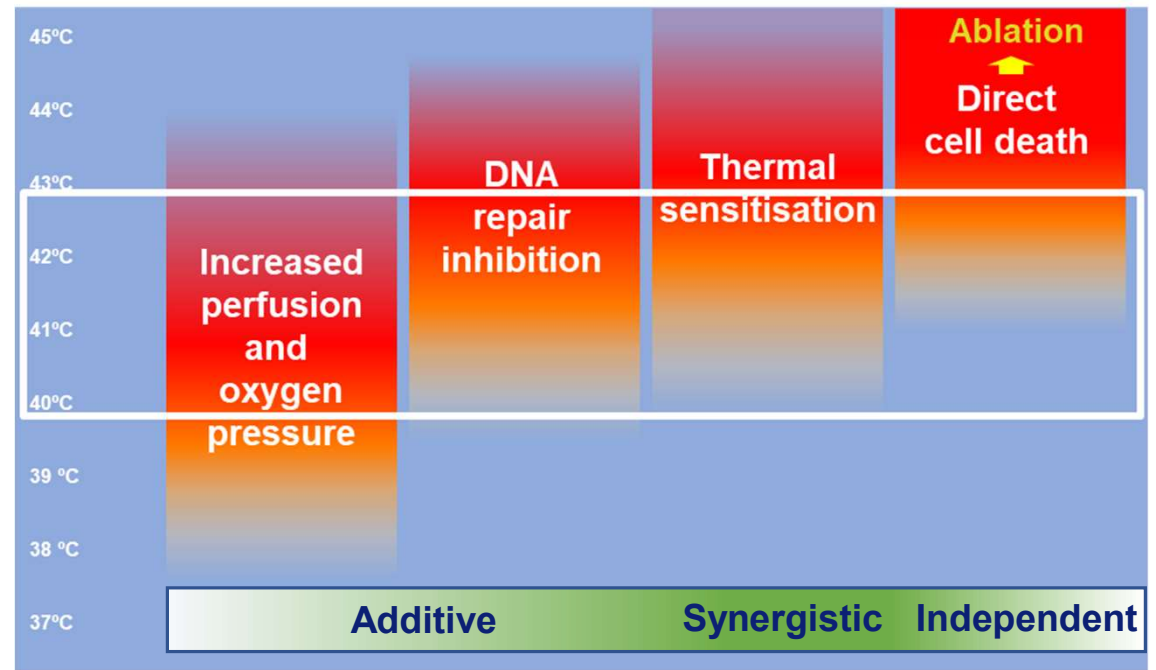
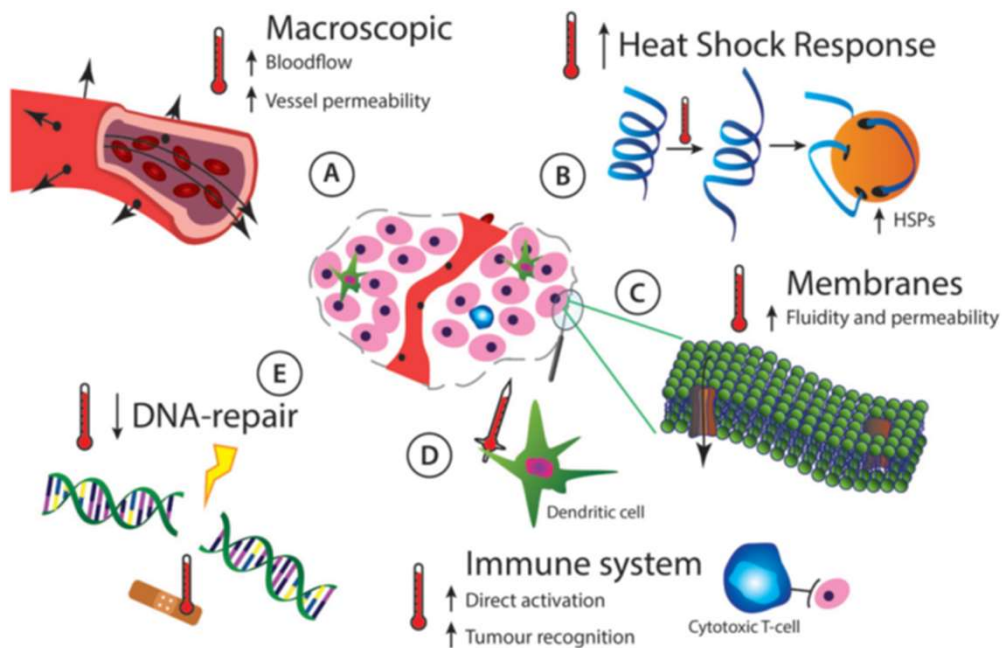
# Biological mechanisms of hyperthermia



Van den Tempel et al.  
Int. J. Hyperthermia 2016

# Current biological understanding of Hyperthermia

Plethora of biological effects, each with a specific temperature range

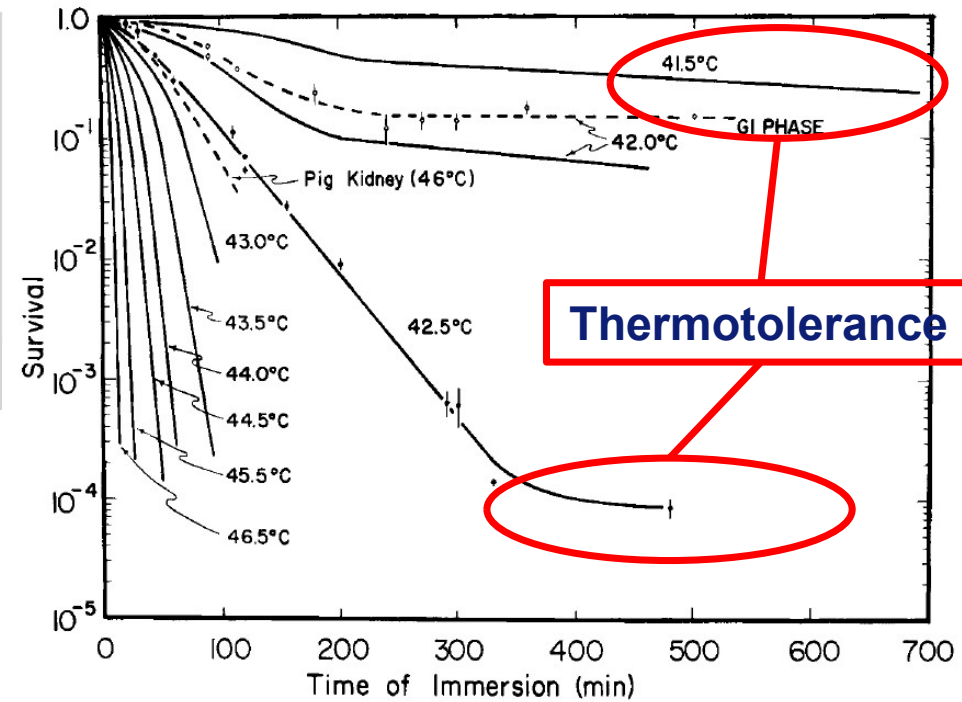
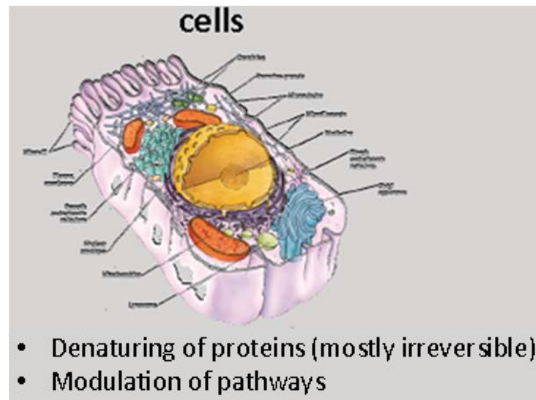
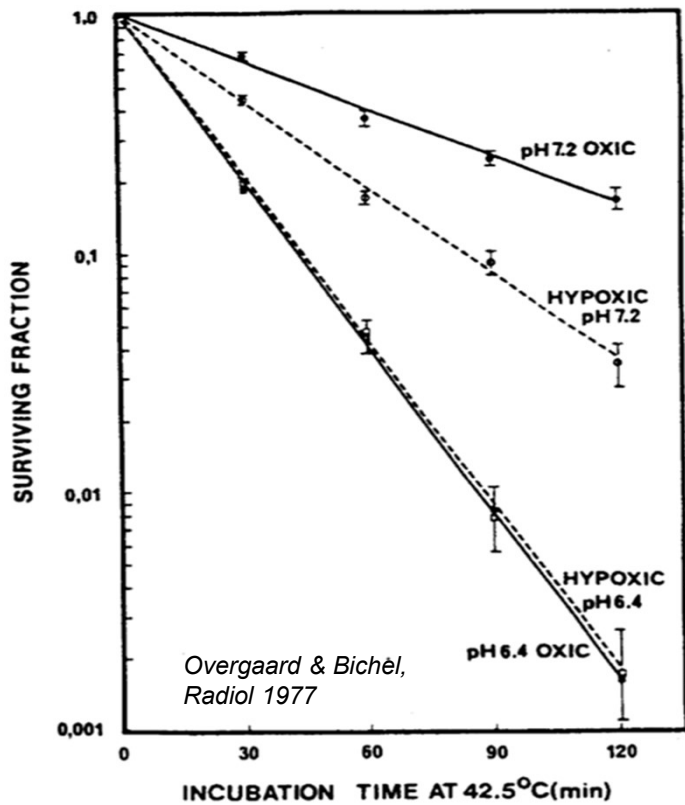


# Levels of interaction hyperthermia with radiotherapy or chemotherapy

- 1. Independent: hyperthermia and RT/CT appear to act by independent mechanisms.**
- 2. Additive: hyperthermia results in additional damage. With increasing temperature, the effectiveness of the cytotoxic mechanism is enhanced.**
- 3. Synergistic: thermal sensitization to known effects occur with increasing temperature.**

# Independent interaction HT with RT or CT

## Direct Cell death



Survival curves for asynchronous Chinese hamster ovary (CHO) cells heated at different temperatures for varying lengths of time.

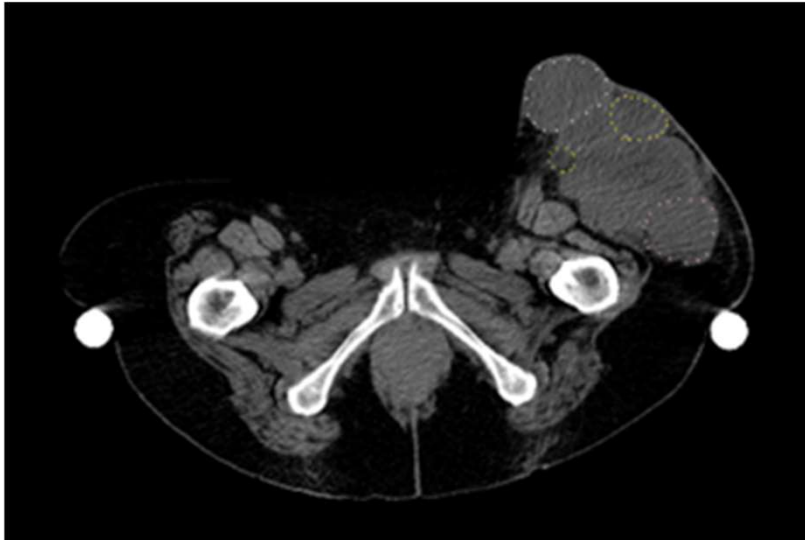
Dewey, Int. J. Hyperthermia 1994

Erasmus MC

*Erasmus*

# Independent interaction HT with RT or CT

## Direct Cell death

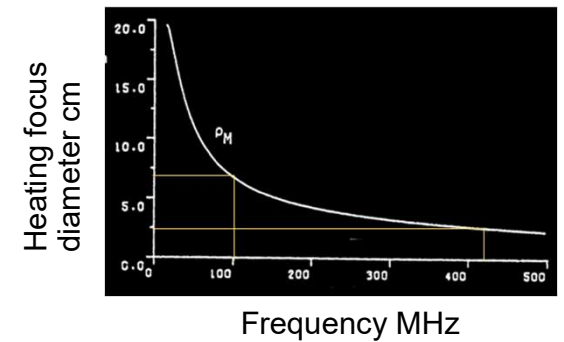
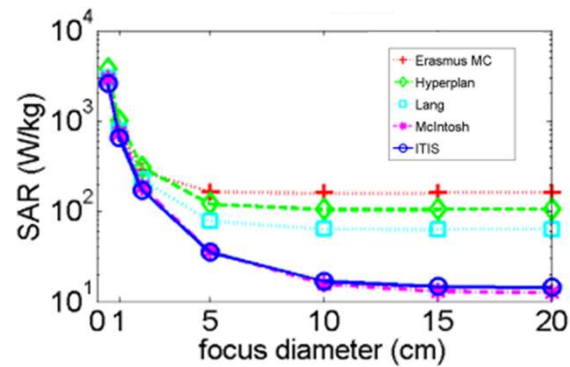


Hypoxic areas are easily heated

Large hypoxic volume: Yes

Small areas: No

Small tumors require high SAR in order to heat



Adibzadeh et al. IJHT2018

# Levels of interaction hyperthermia with radiotherapy or chemotherapy

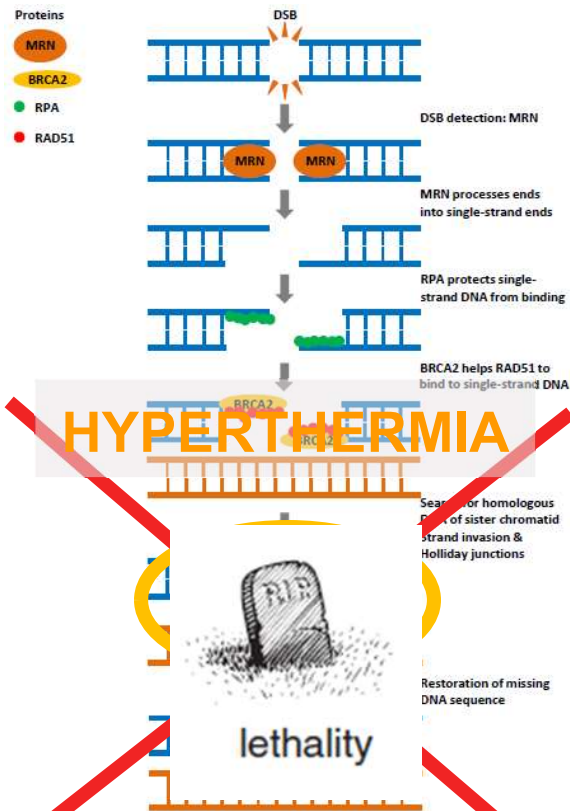
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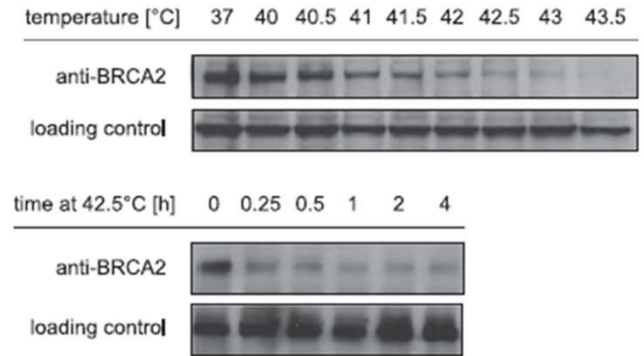
3. Synergistic: thermal sensitization to known effects occur with increasing temperature.

# Additive interaction HT with RT or CT

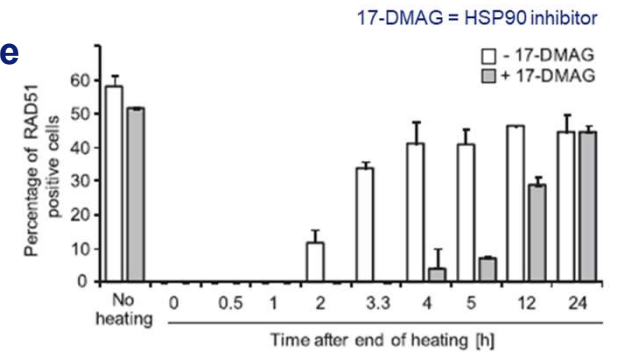
## Blocking DNA-damage repair



Thermal dose dependent



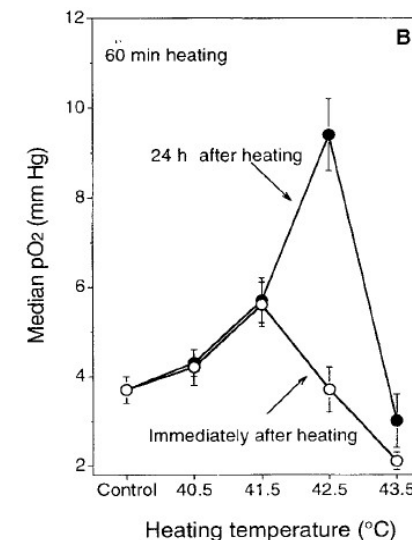
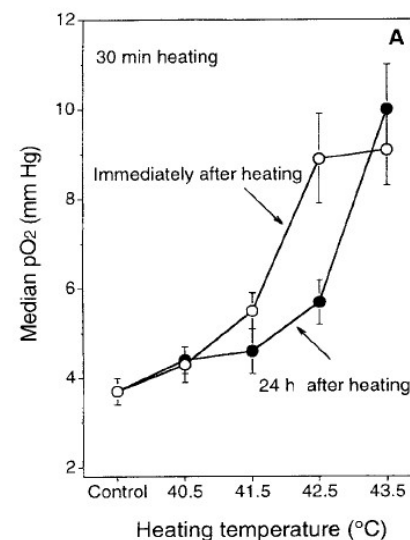
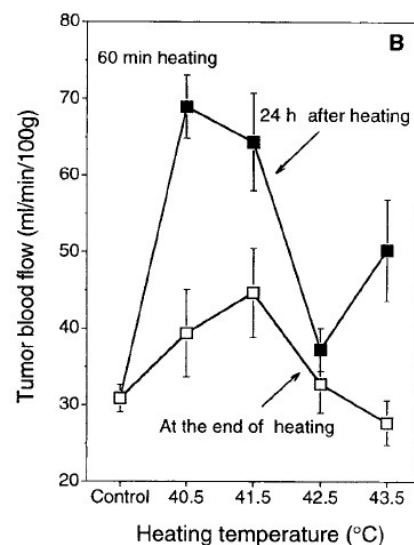
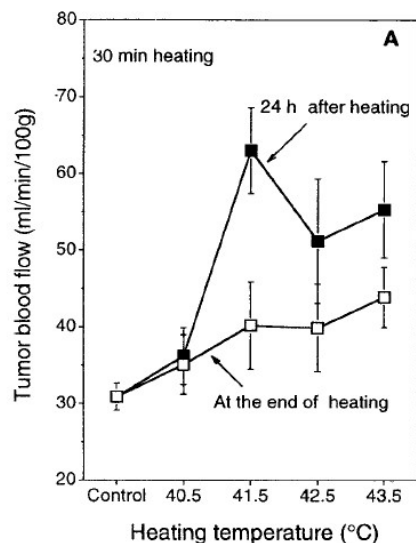
Effect decreases over time





# Additive interaction HT with RT or CT

## Enhanced perfusion and pO<sub>2</sub>



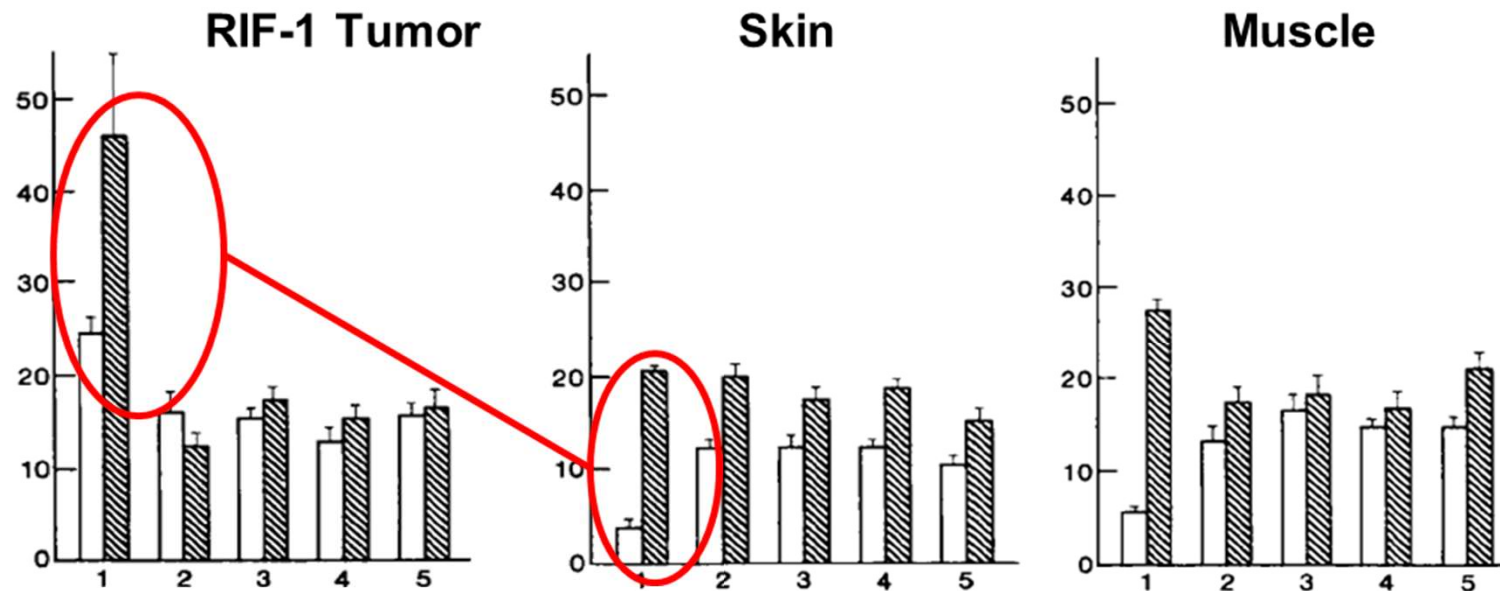
Tumor blood flow in control and treated R3230 Ac tumors measured immediately after or 24 h after heating at various temperatures for 30 min (panel A) and 60 min (panel B). Means  $6 \pm 1$  SEM of 9–23 tumors are shown.

Median tumor  $pO_2$  in control and treated R3230 Ac tumors measured within 12–15 min or 24 h after heating at various temperatures for 30 min (panel A) and 60 min (panel B). Each point represents the mean  $6 \pm 1$  SEM of 10–26 tumors.

# Additive interaction HT with RT or CT

## Enhanced perfusion and pO<sub>2</sub>

### Differential effect: tumour and normal tissue

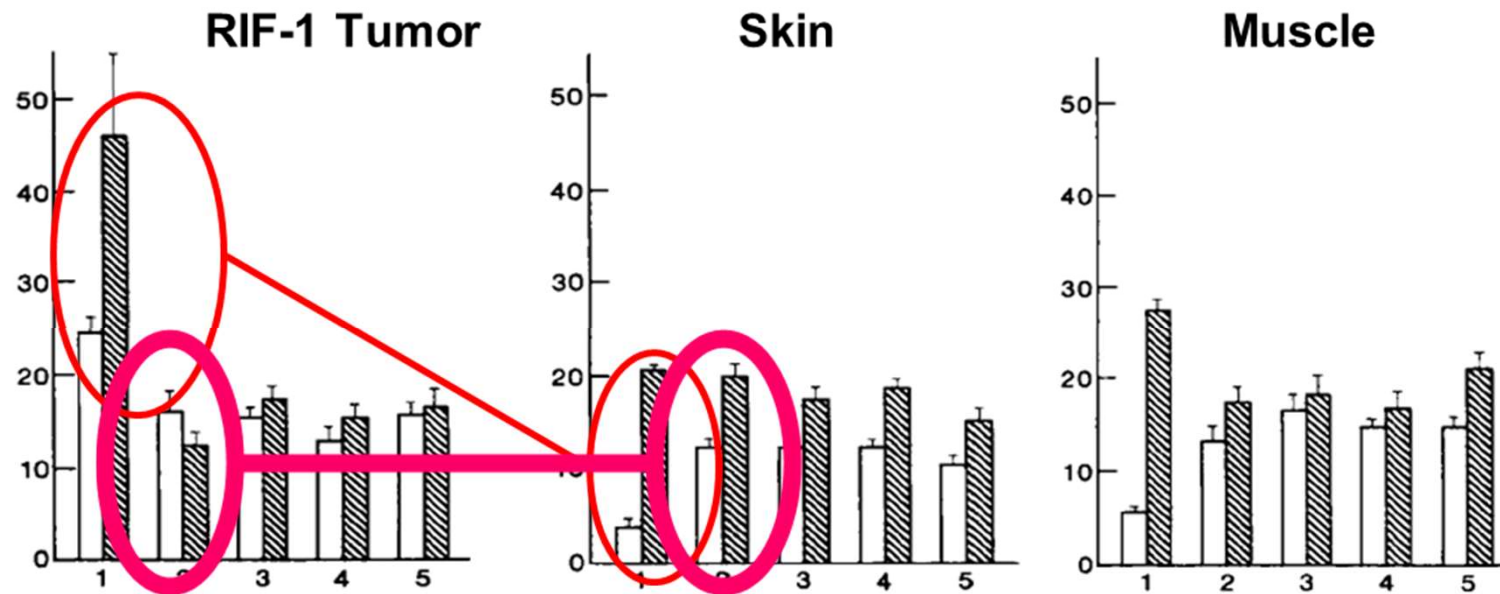


Number of heating at 43.5°C, 60 min., with an interval of 3 days between each heating  
Large difference between initial perfusion values tumor vs normal tissue. Normal tissue has relative, a much larger increase in perfusion.

# Additive interaction HT with RT or CT

## Enhanced perfusion and pO<sub>2</sub>

### Differential effect: tumour and normal tissue



Number of heating at 43.5°C, 60 min., with an interval of 3 days between each heating. Large difference between initial perfusion values tumor vs normal tissue. Normal tissue has a much larger increase in perfusion.

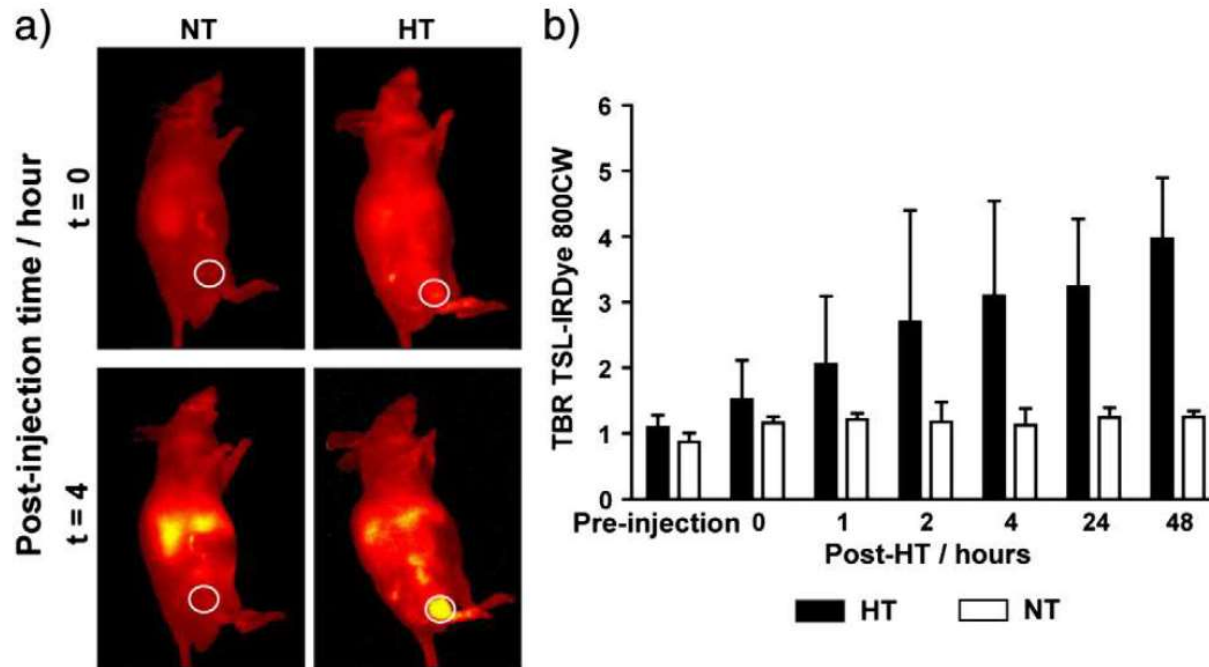
**Tumor loses its ability to respond on heat load and normal tissue has a higher initial perfusion.**



# Additive interaction HT with RT or CT

## Enhanced vascular leakage in tumors

Mild hyperthermia augments liposome accumulation

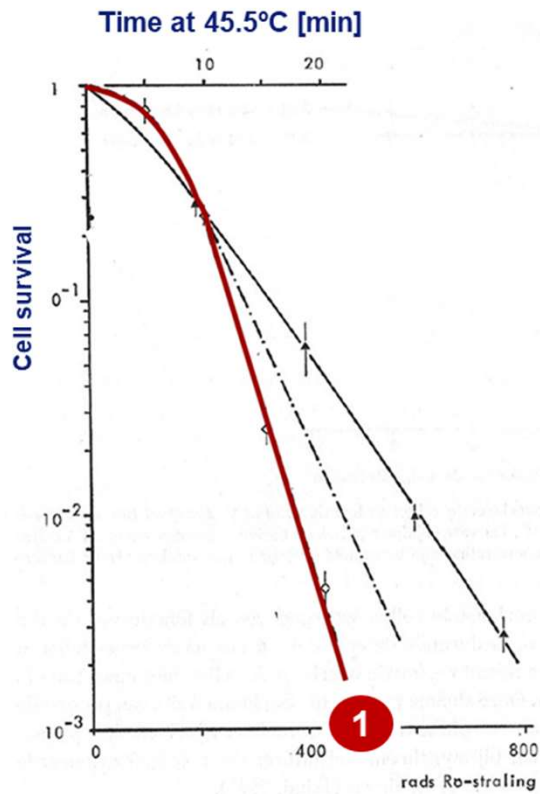


# Levels of interaction hyperthermia with radiotherapy or chemotherapy

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# Synergistic interaction HT with RT

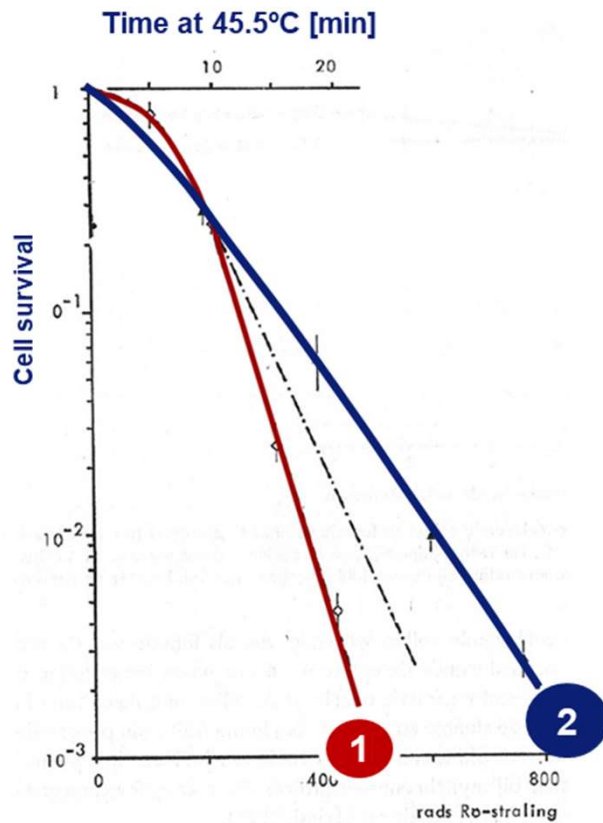
## Radiosensitization



1 Heat alone

# Synergistic interaction HT with RT

## Radiosensitization



1

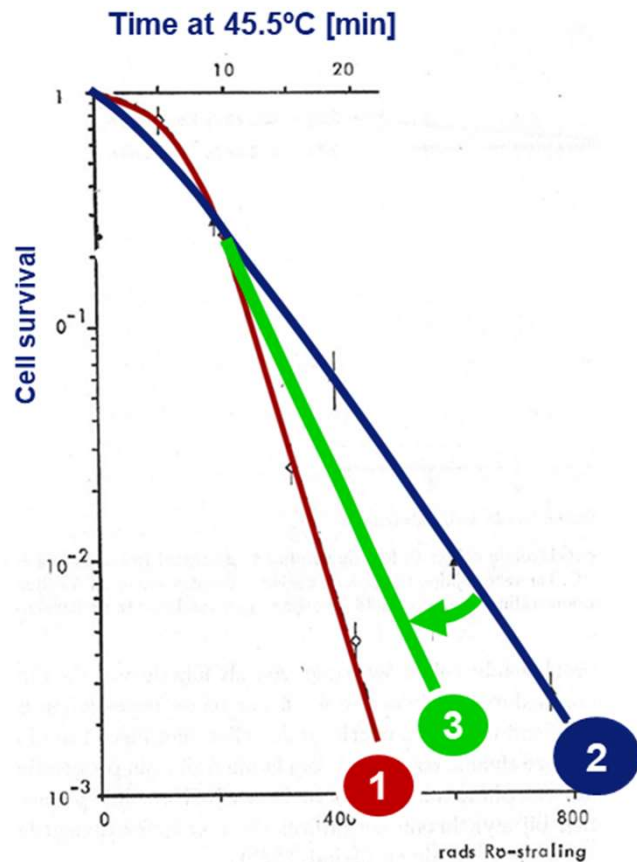
Heat alone

2

Radiation alone

# Synergistic interaction HT with RT

## Radiosensitization



1

Heat alone

2

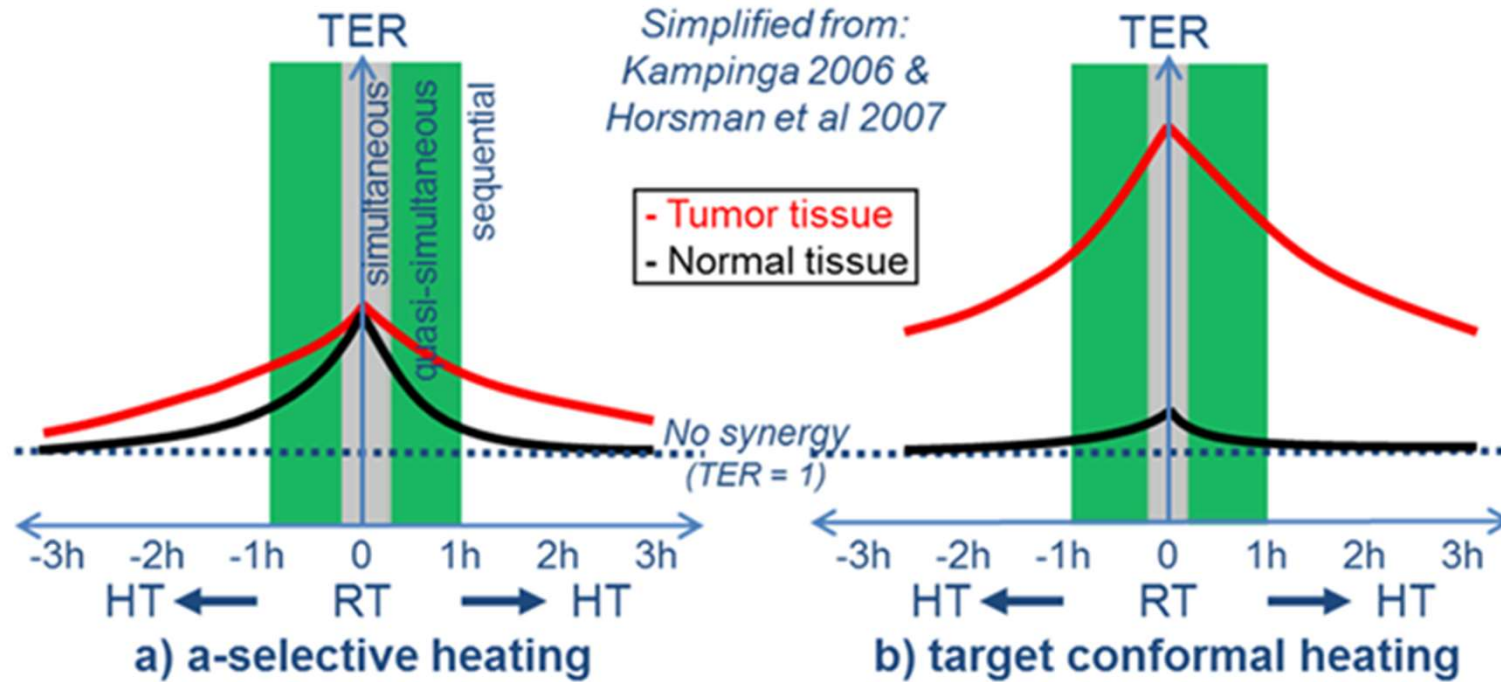
Radiation alone

3

Heat plus Radiation



# Additive and synergistic interaction hyperthermia with radiotherapy: depends on thermal dose & interval time



# Synergistic interaction HT with CT

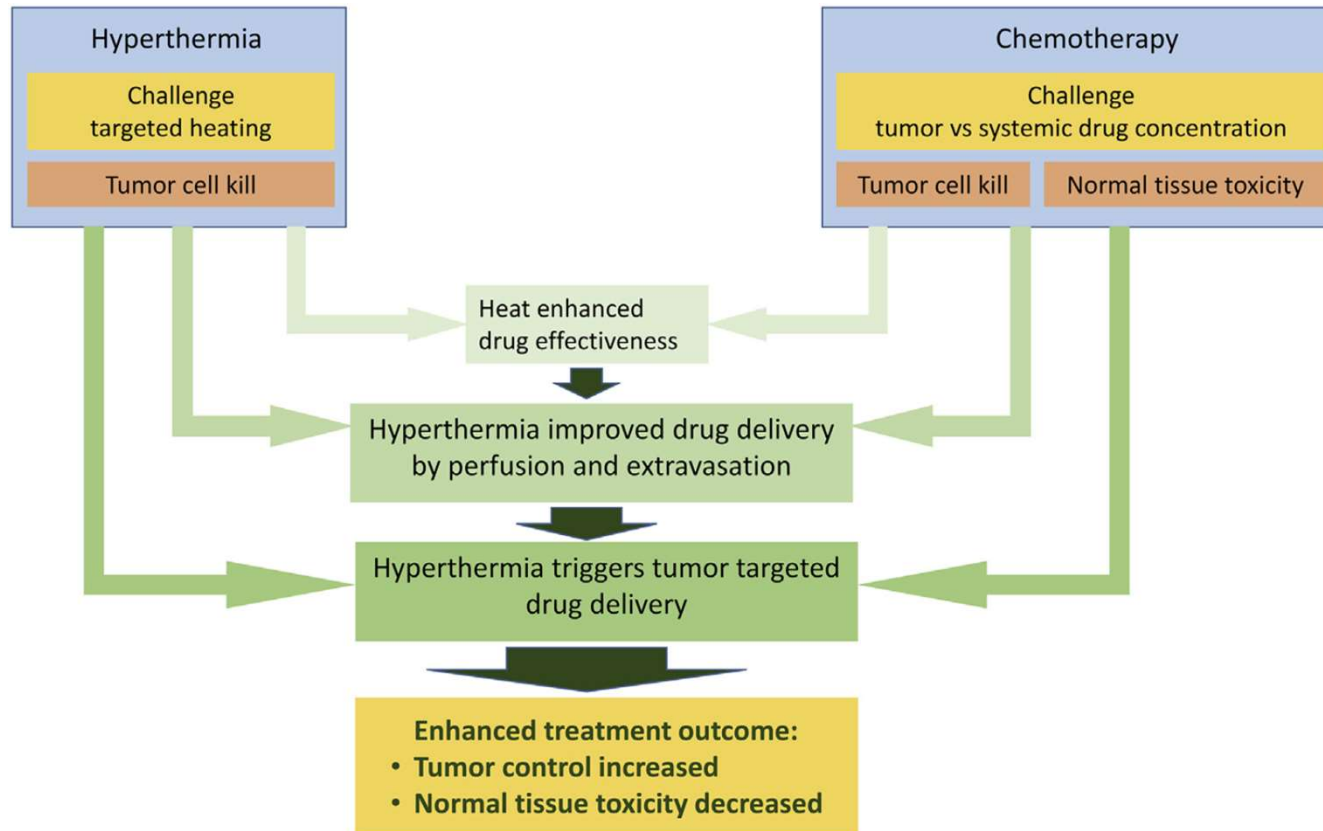
## Chemosenstization

Thermal enhancement ratio for various chemotherapeutics and as function of temperature for a F5a-II and mammary tumor.

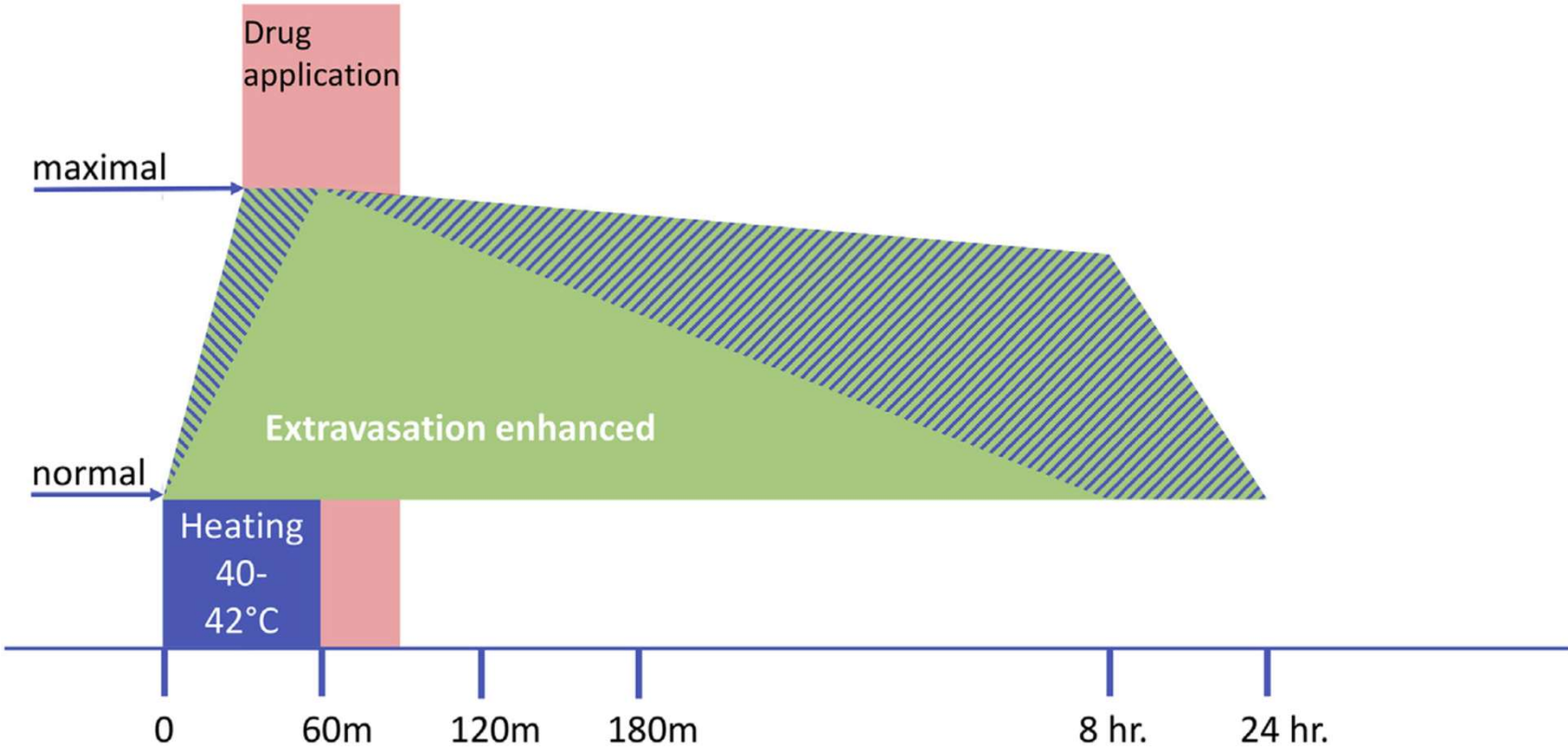
Temperature [°C]	Thermal enhancement ratio (TER)			
	40-42	42.5-44	40-42	42.5-44
Tumortype	F5a-II		Mammary Ca	
Drug				
Cisplatin	1.5 ± 0.2	1.6 ± 0.2	2.9	3.6
Cyclophosphamide	2.3 ± 0.3	2.7 ± 0.4		1.6 ± 0.1
Ifosfamide (30 min)	1.5 ± 0.3			
Ifosfamide (90 min)	3.6 ± 0.5			
Melphalan	3.6 ± 0.5			
BCNU	2.3 ± 0.2	2.7 ± 0.2		
Bleomycin	1.2 ± 0.4	1.7 ± 0.3		
Mytomyacin C	1.0			2.8 ± 0.5
5-Fluorouracil	1.0	1.0		
Doxorubicin	1.0	1.0	1.0	1.0

Data taken from Urano et al. [90].

# Thermo-Chemotherapy: levels of interaction



# Interaction hyperthermia with chemotherapy: relevance of Interval time



# Conclusion levels of interaction hyperthermia with radiotherapy or chemotherapy

## All three levels

- Independent
- Additive
- Synergistic

of interaction between hyperthermia and RT or CT may occur.

The relevant contribution of each interaction depends on the applied thermal dose as well as on the correct sequence and time interval between HT and RT or CT



# Questions?

