Biological basis for combining hyperthermia with radiotherapy or chemotherapy

Michael R. Horsman, BSc, PhD, DMSc

Professor of Experimental Radiotherapy

Experimental Clinical Oncology-Dept. Oncology
Aarhus University Hospital
Aarhus, Denmark.

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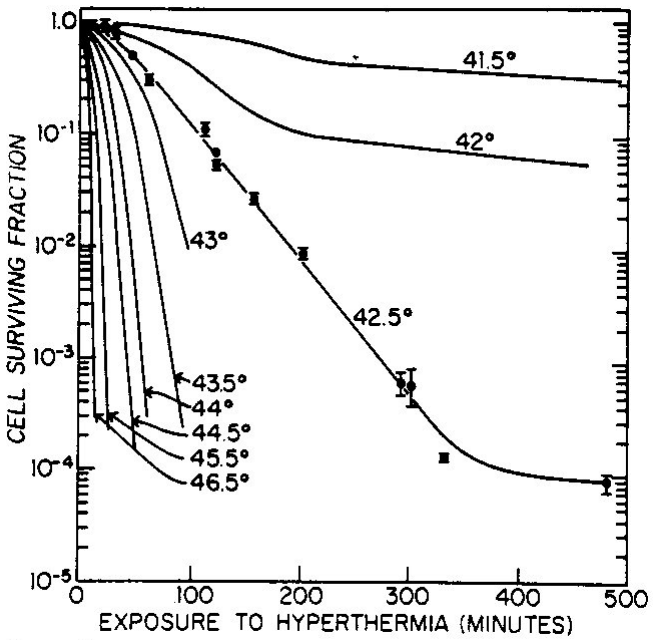
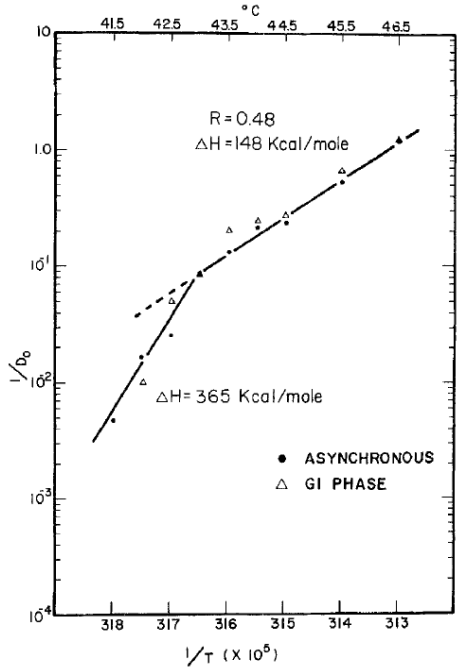
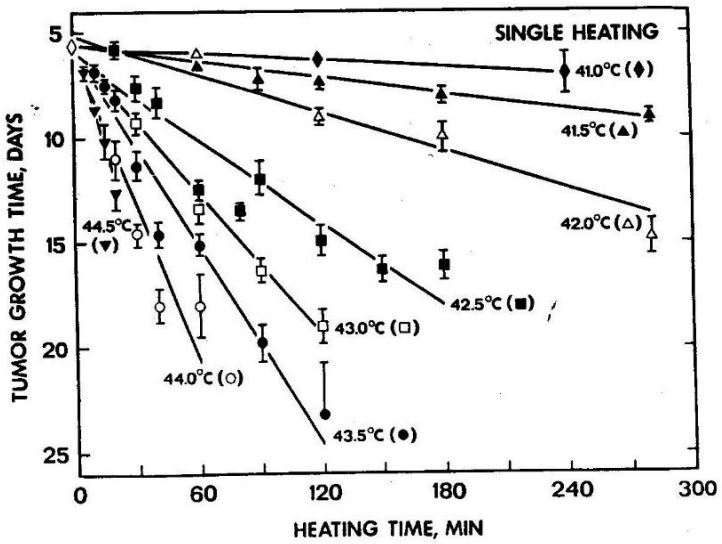
Fever range: 37-42°C
Hyperthermia: 40-45°C
Thermal ablation: >45°C

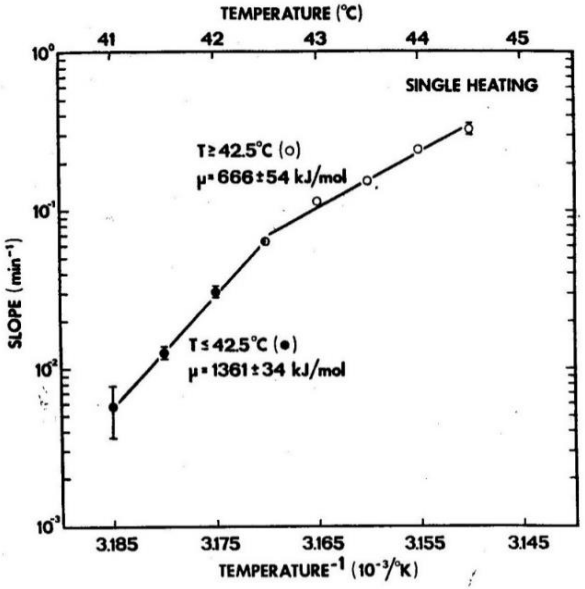
Cell killing by heat





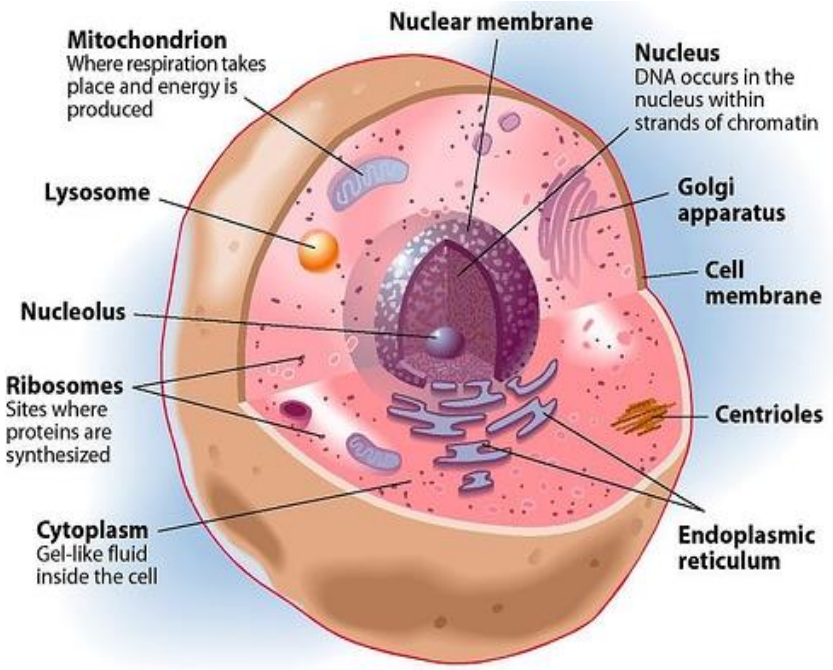
Dewey et al., Radiol (1977) 123:463-474





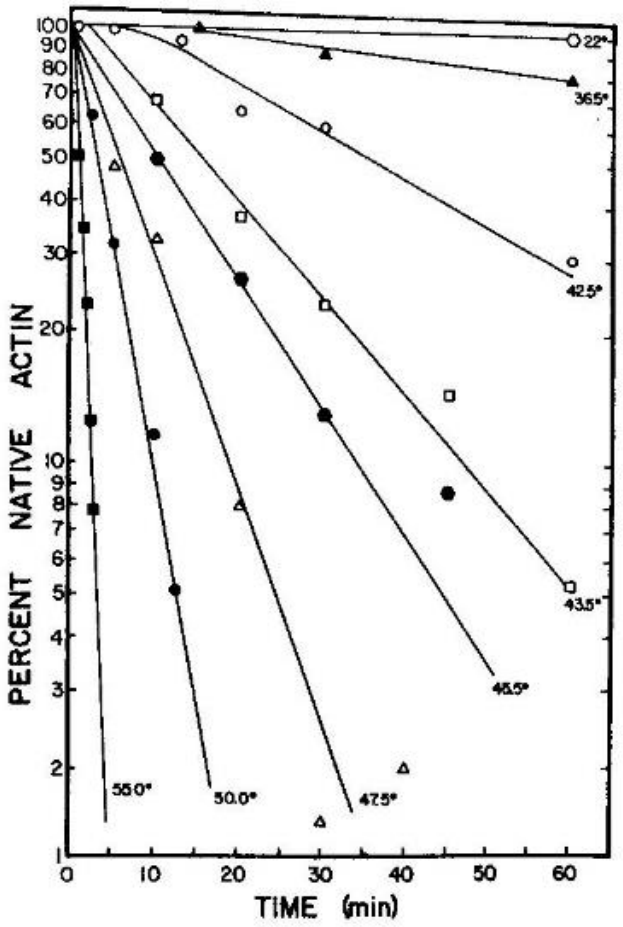
Lindegaard & Overgaard (1987) Int. J. Hyperthermia 3:79-81

Targets for heat



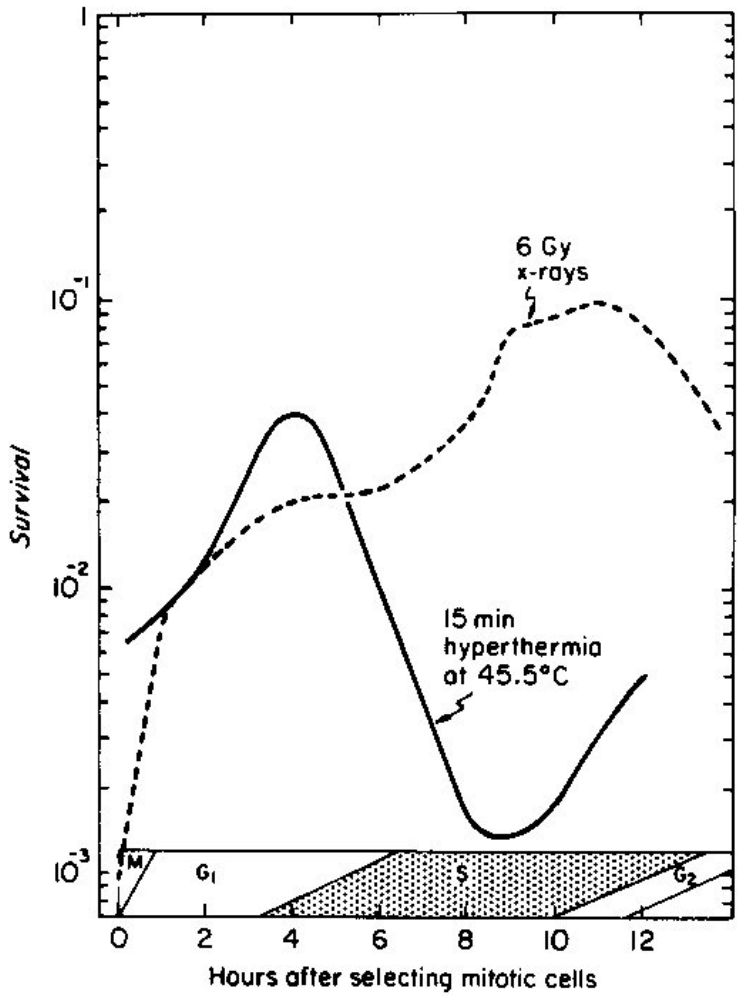
- **Membranes** - **lipids**
  - **proteins**
- **Cytoskeleton** - **microfilaments**
  - **microtubules**
- **Cytosol** - **mitochondria**
  - **lysosomes**
  - **respiration/glycolosis**
  - **protein synthesis**
- **Nucleus** - **DNA replication**
  - **RNA synthesis**
  - **chromosomal damage**

Protein inactivation



Heacock et al. (1982)
JNCI 61:73-75

Cell cycle



Dewey et al. (1977)
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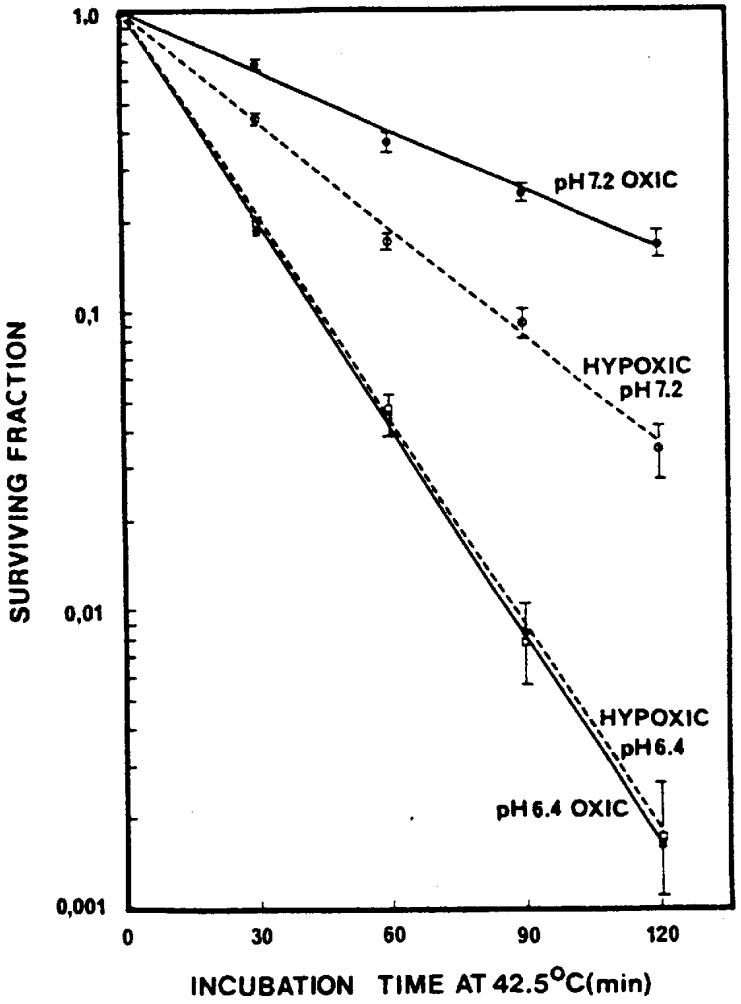
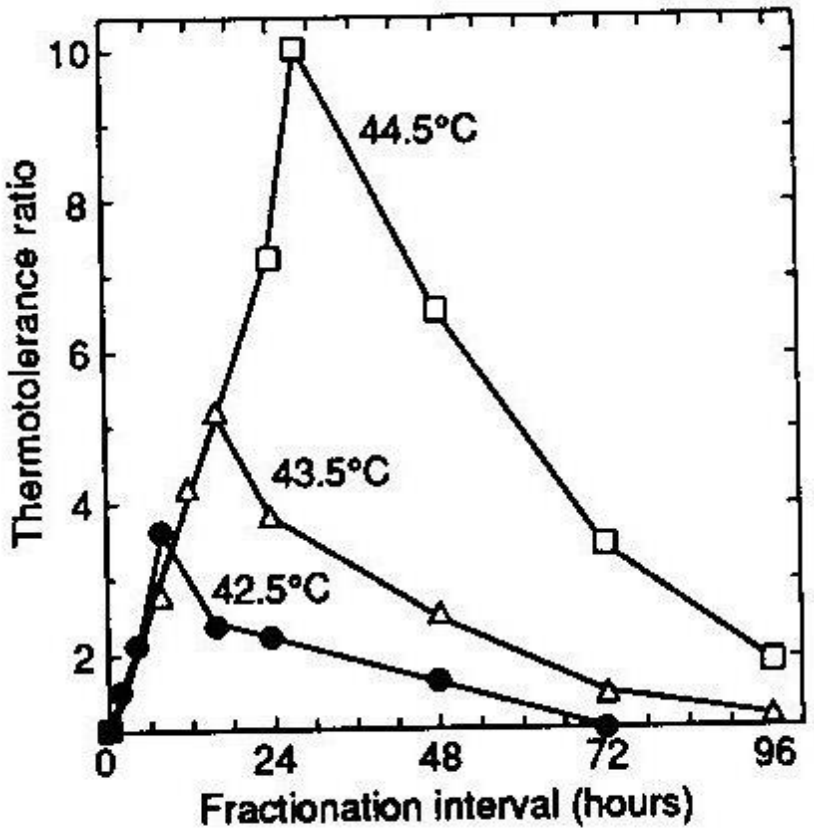
Hypoxia and pH



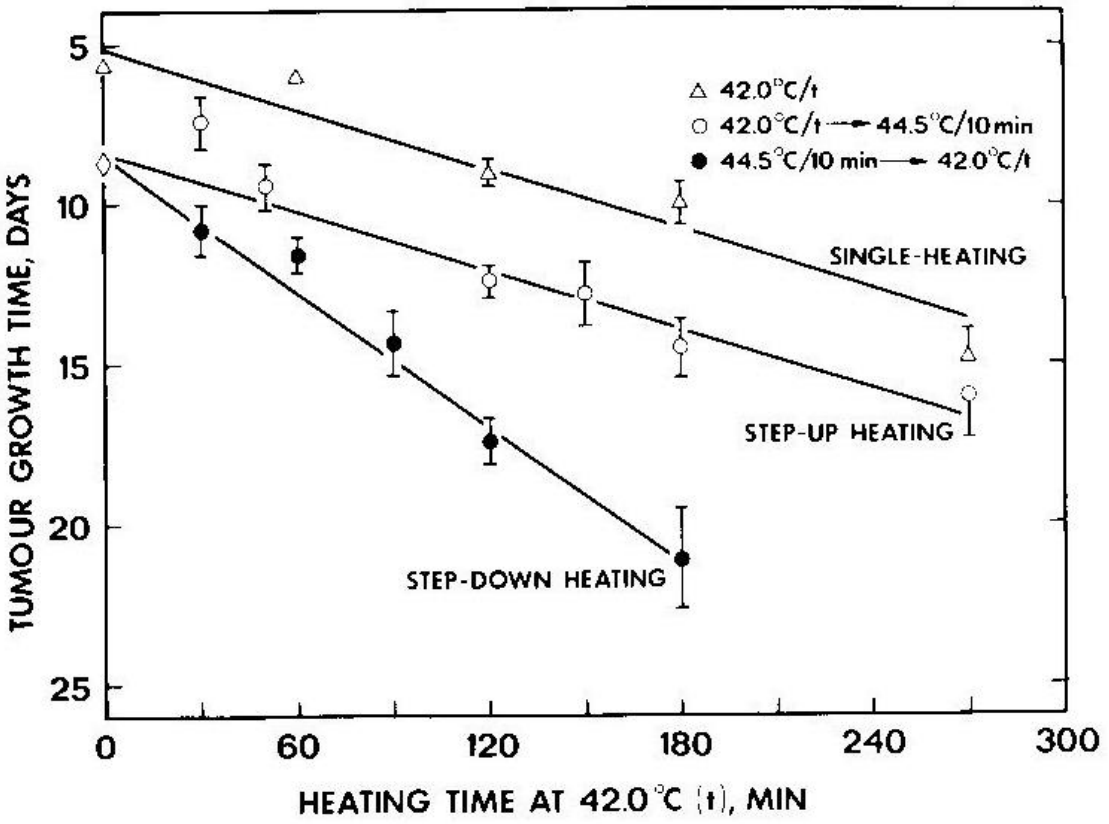
Overgaard & Bichel (1977)
Radiol. 123:511-514

Thermotolerance



Overgaard (1989) Int. J. Radiat. Oncol. Biol. Phys. 16:535-543

Step-up/Step-down heating



Lindegaard & Overgaard (1987) Int. J. Hyperthermia 3:79-81

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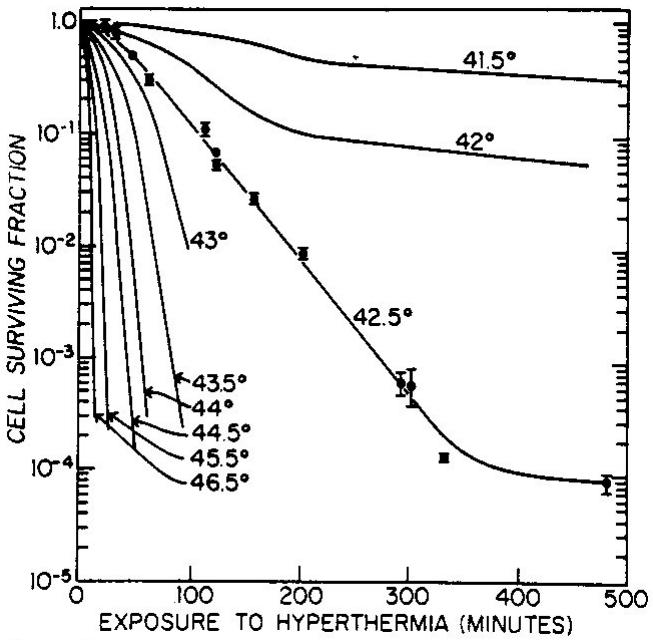

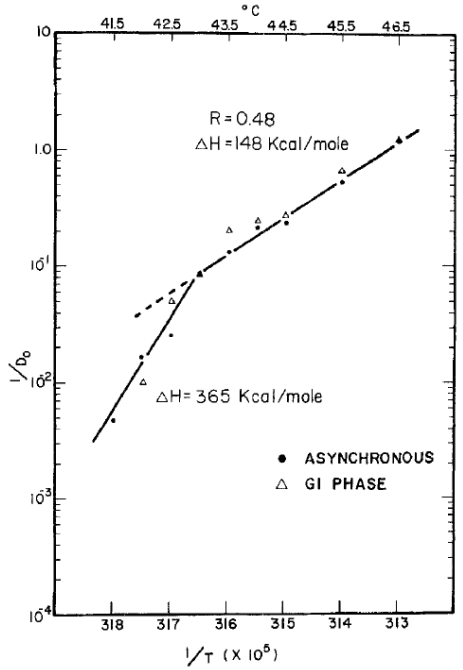

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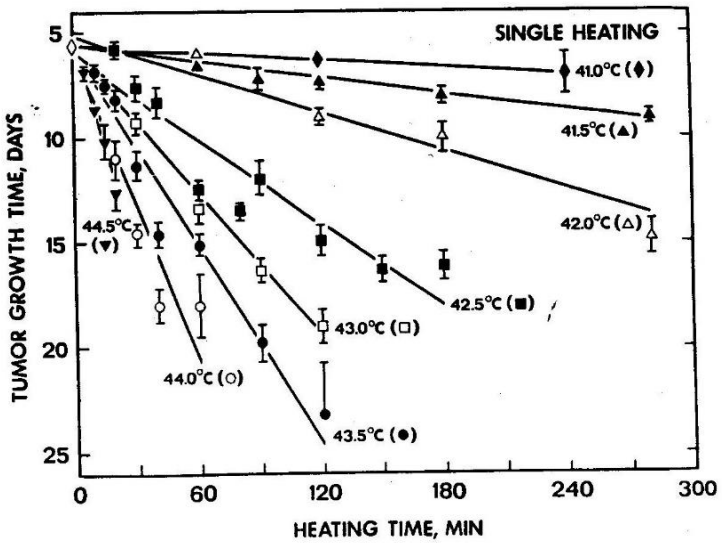
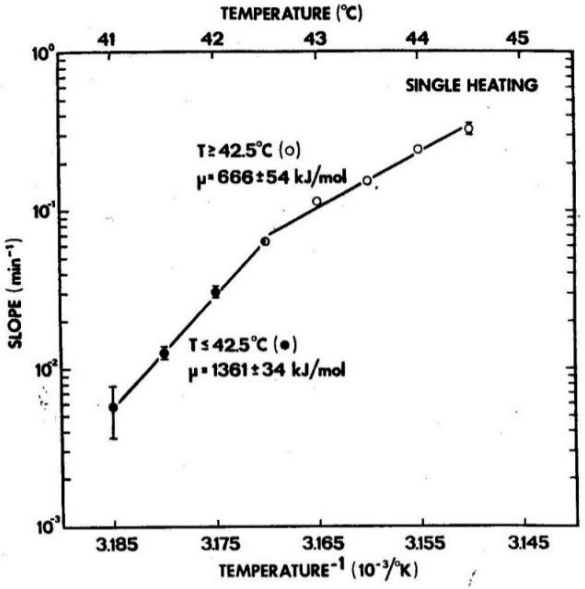
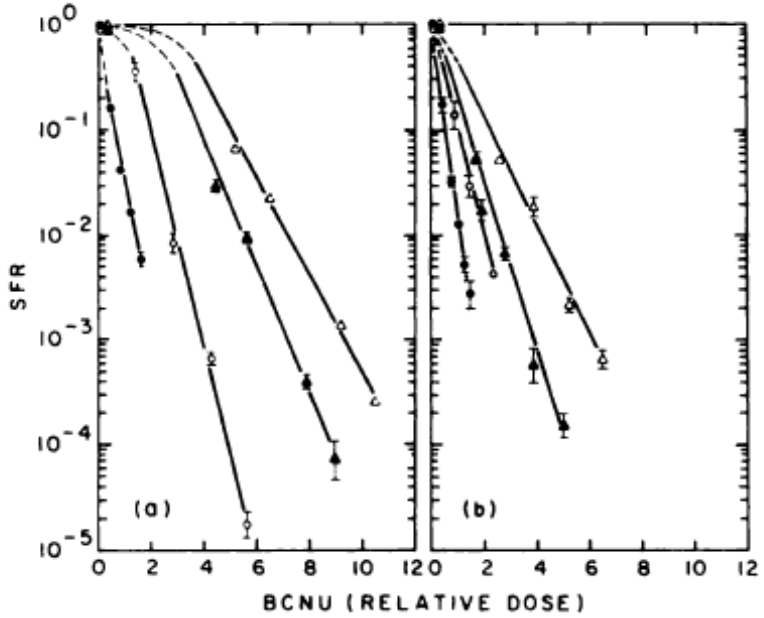


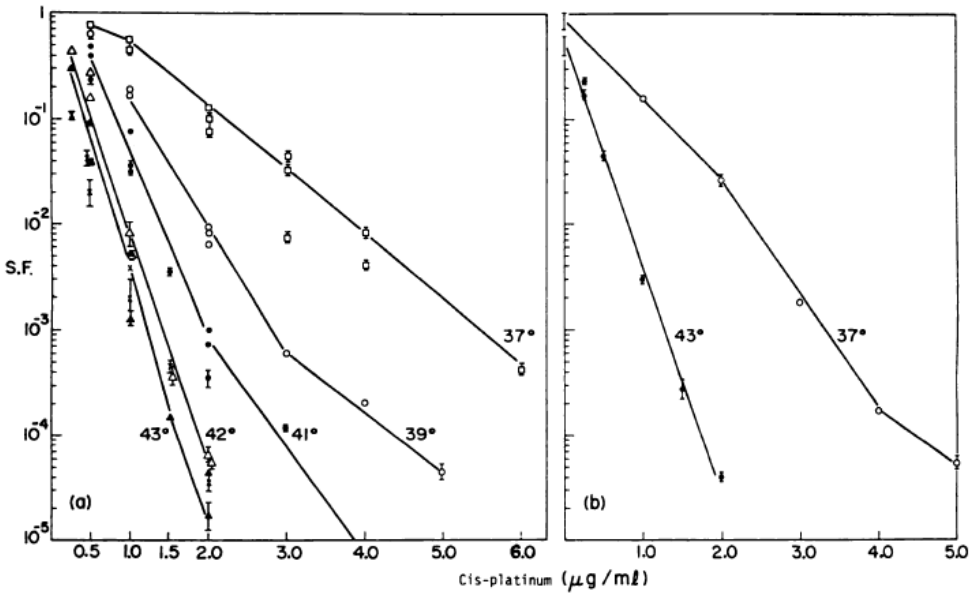


Lindegaard & Overgaard (1987) Int. J. Hyperthermia 3:79-81

Hyperthermia and Chemotherapy

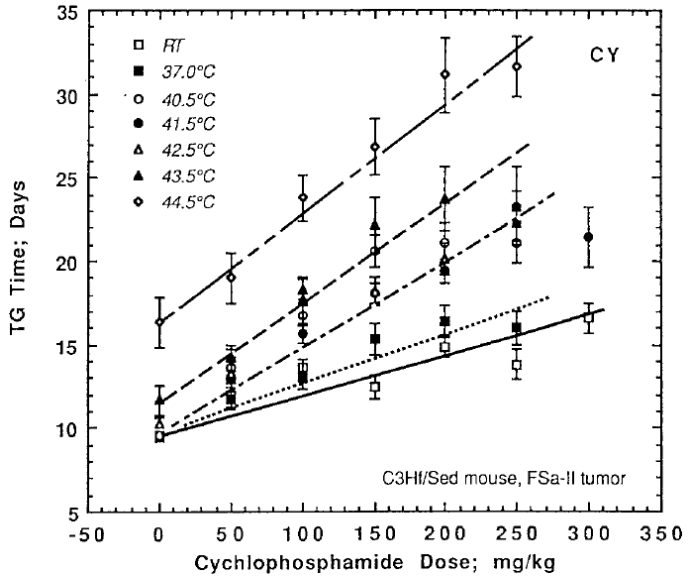
In Vitro





Hahn (1979) Cancer Res. 39:2264-2268

In Vivo

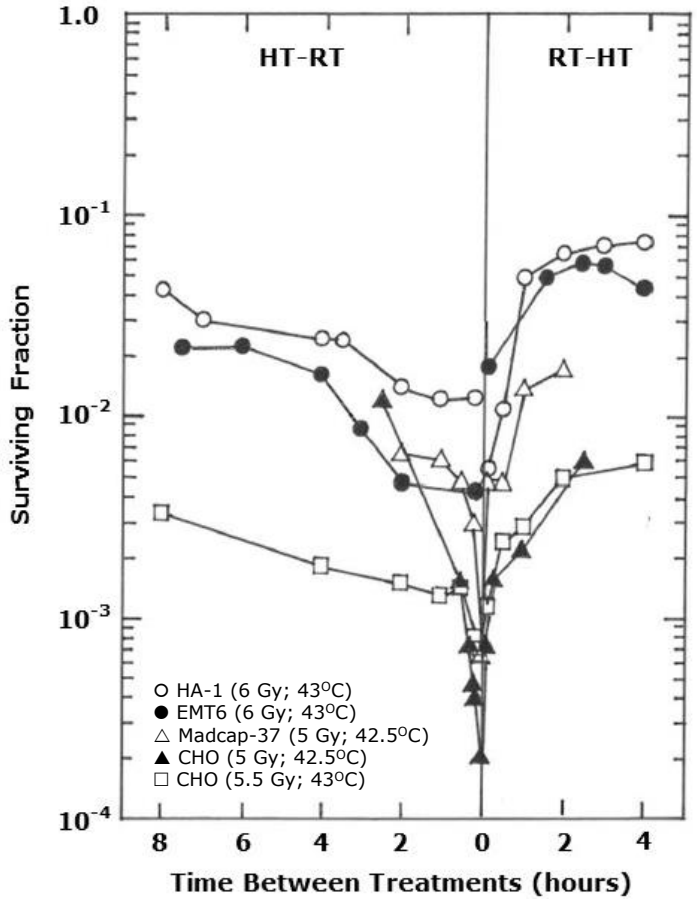


Drug	Treatment Time (min)	TER 41.5°C	TER 43.5°C
5-Fluorouracil	30	1.0	1.0
Adriamycin	30	1.0	1.0
Mitomycin C	30	1.05	---
Bleomycin	30	1.24	1.65
Cisplatin	30	1.48	1.59
Ifosphamide	30	1.52	---
	90	3.60	---
BCNU	30	2.27	2.72
Cyclophosphamide	30	2.28	2.74
Melphalan	30	3.60	---

Urano et al. (1999) Int. J. Hyperthermia 15:79-107

Combining radiation and hyperthermia
Influence of sequence and interval

In vitro cell lines



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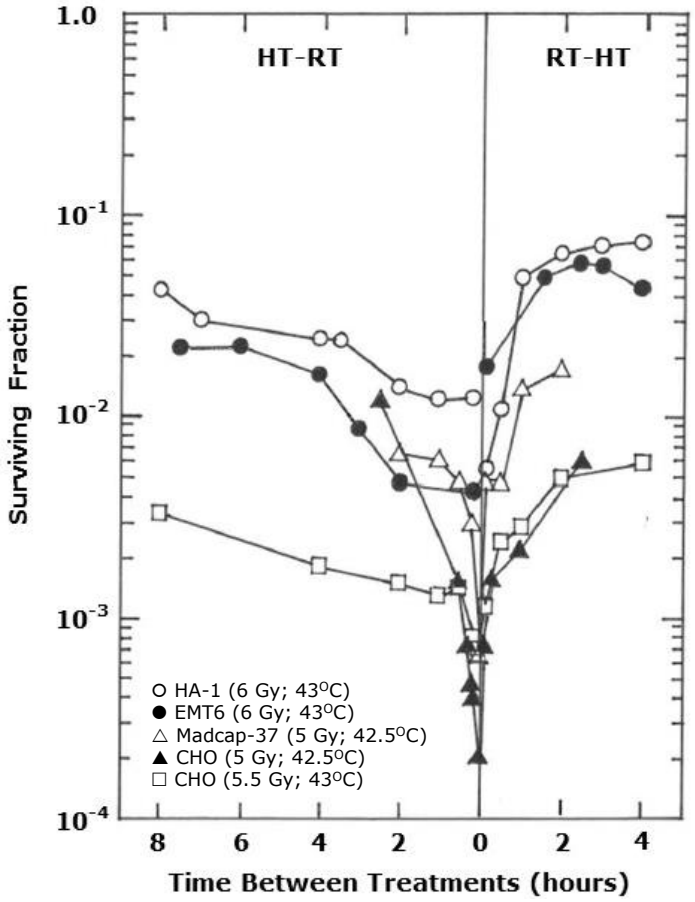
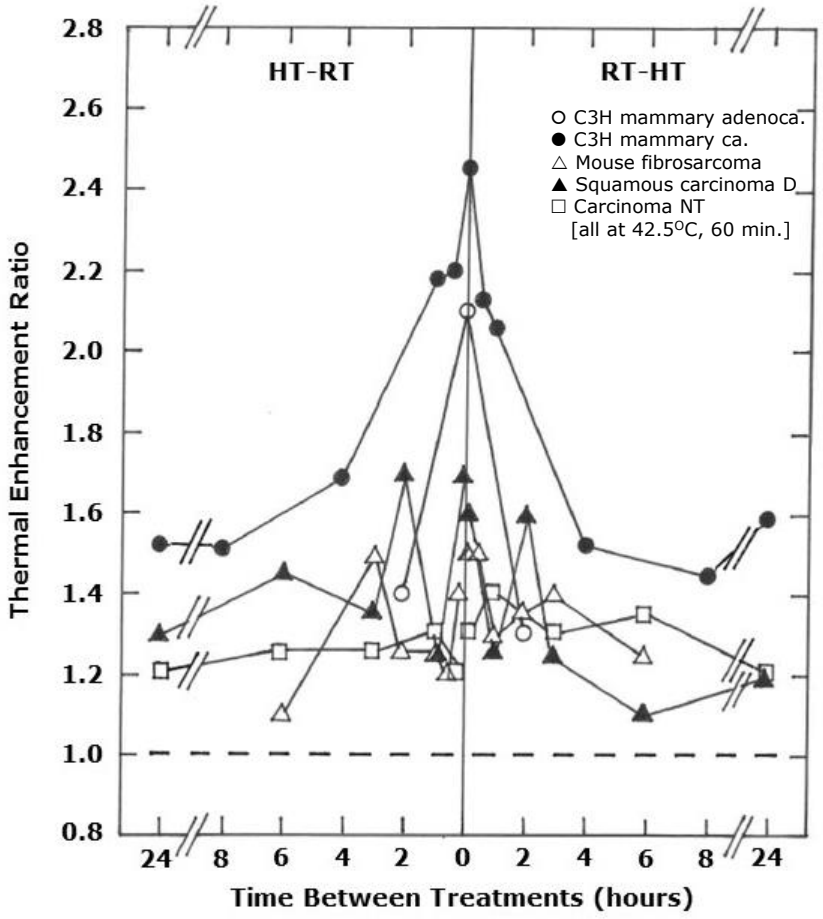


In vivo tumors



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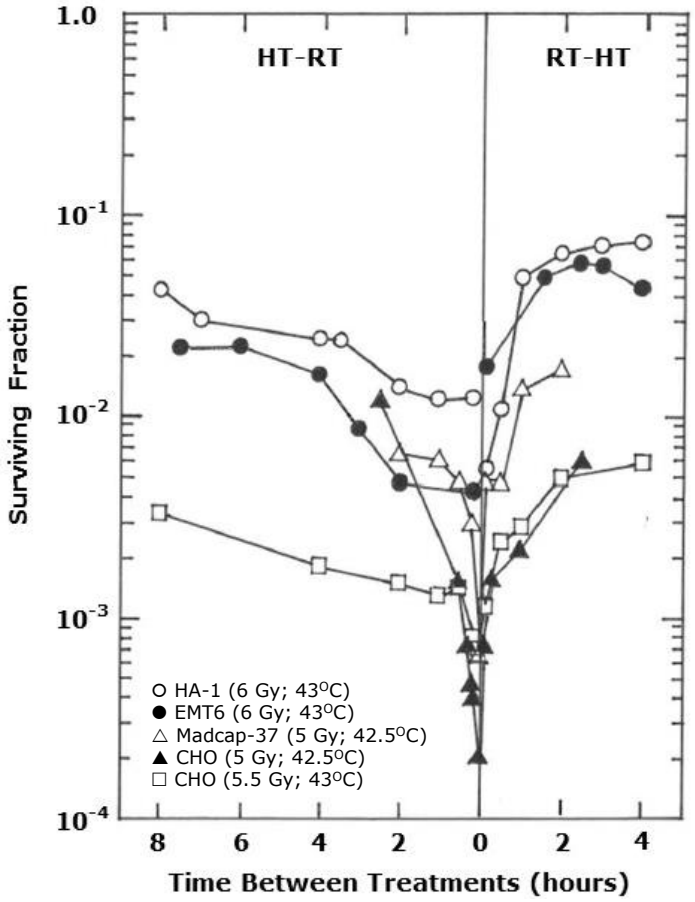
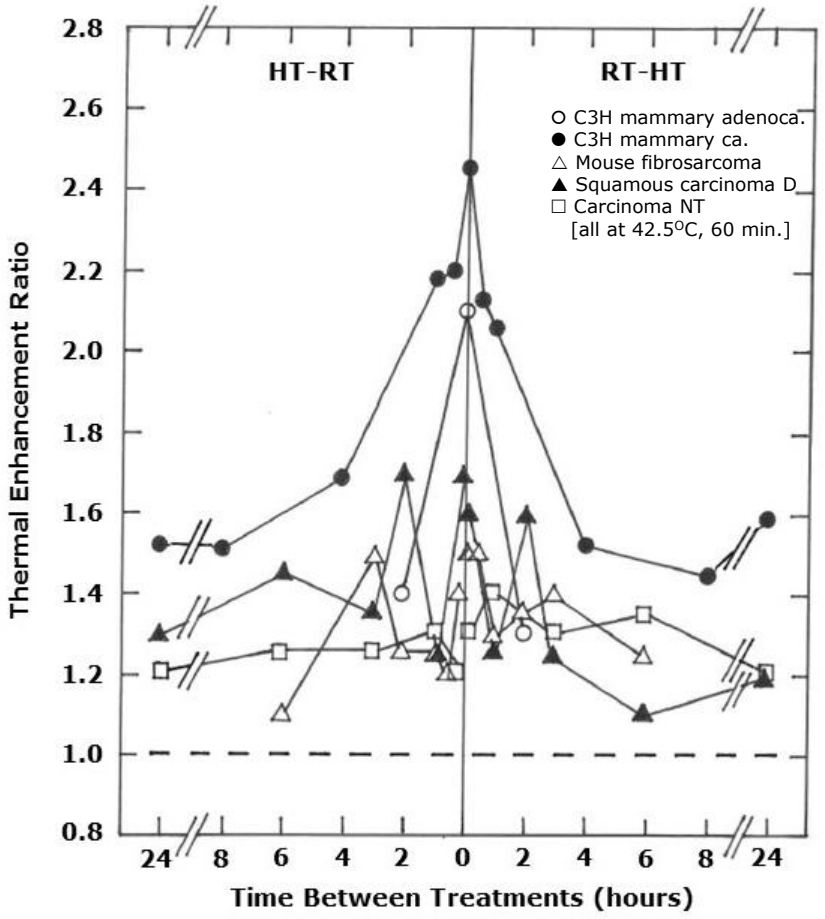
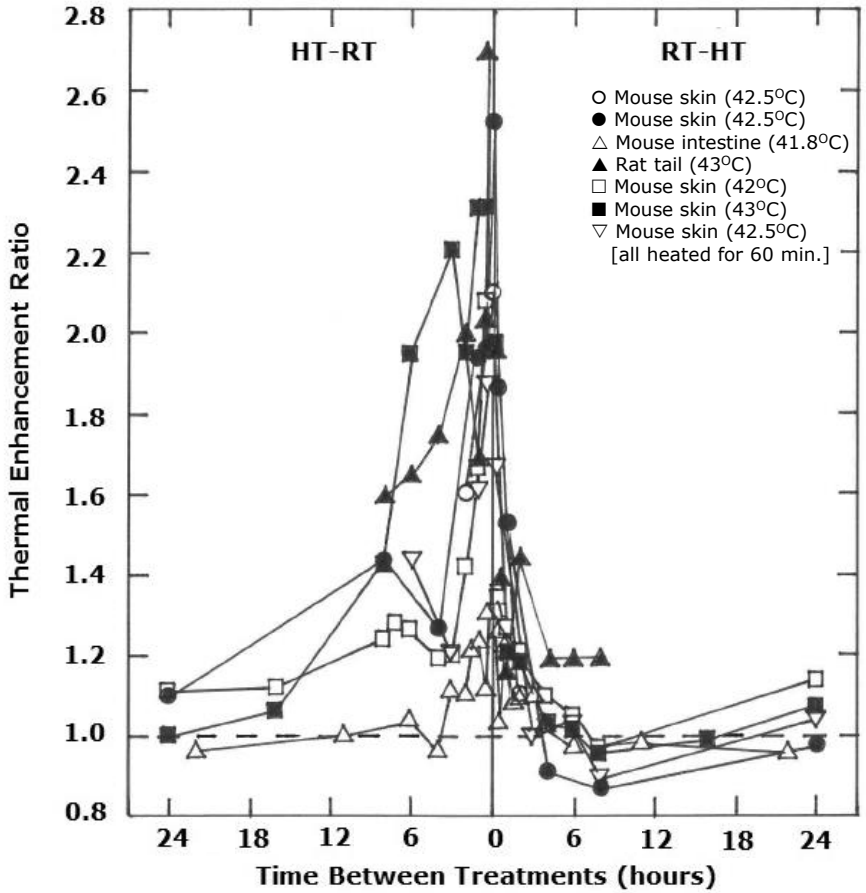


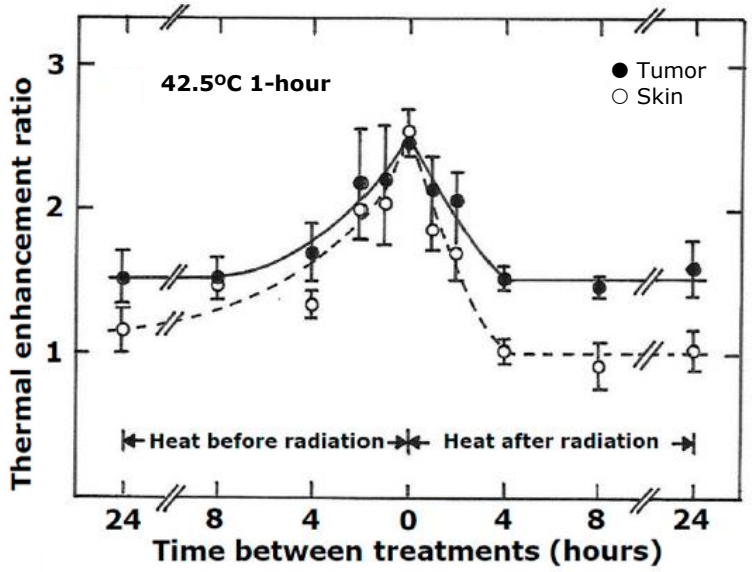
In vivo tumors

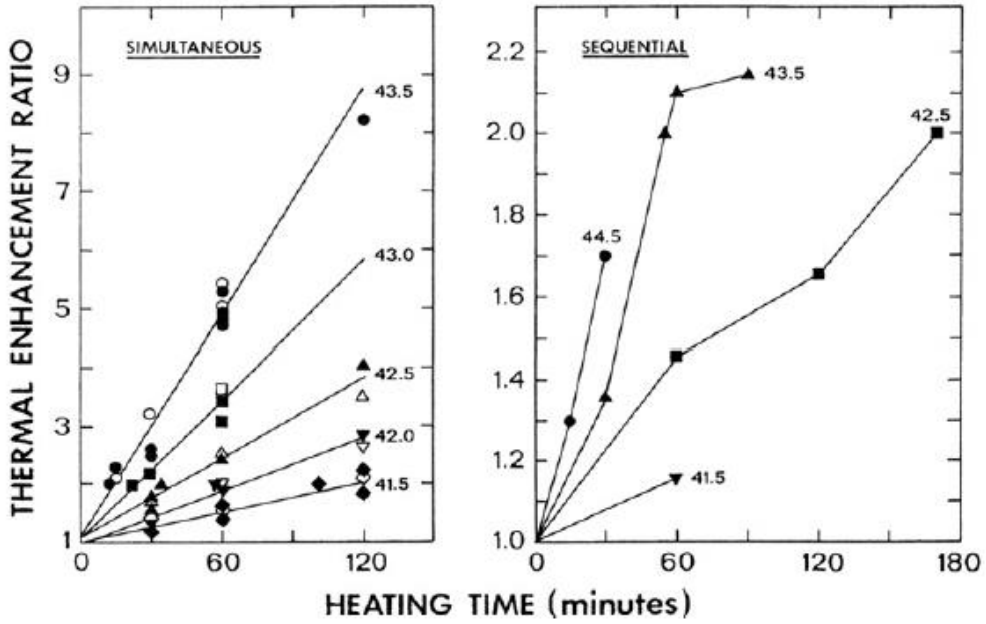


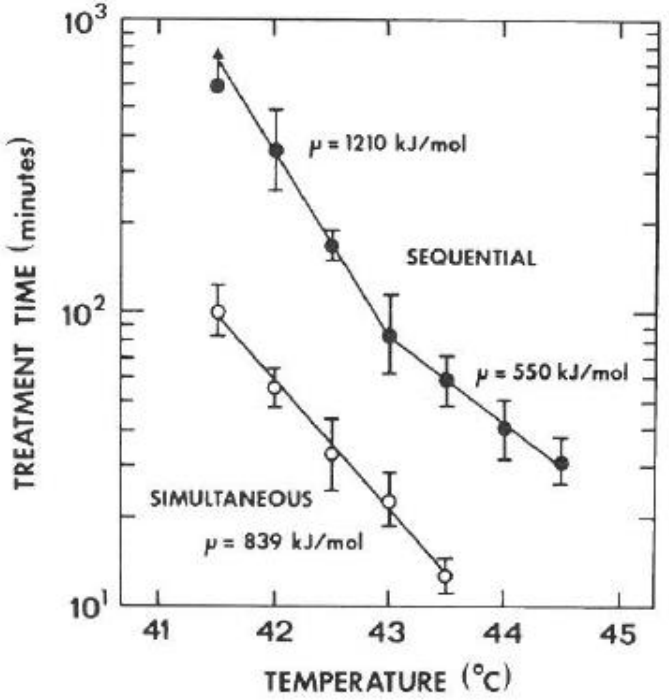
In vivo normal tissues



Importance of heating time and temperature

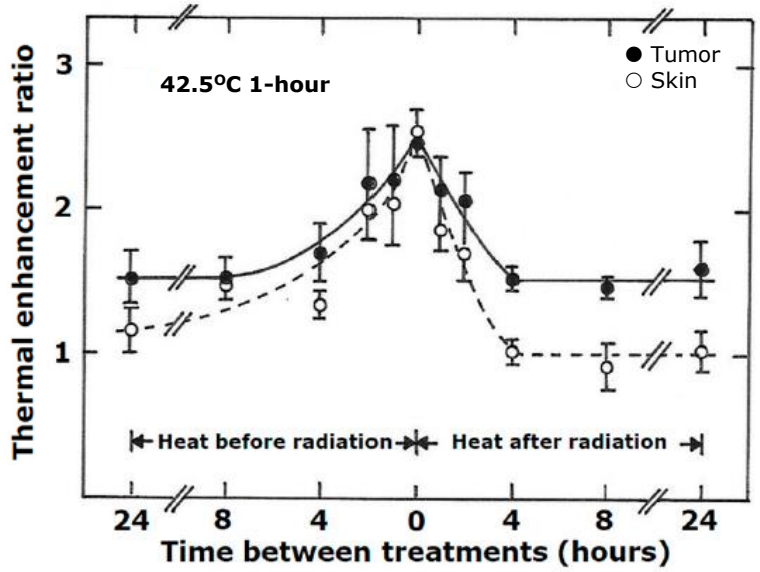




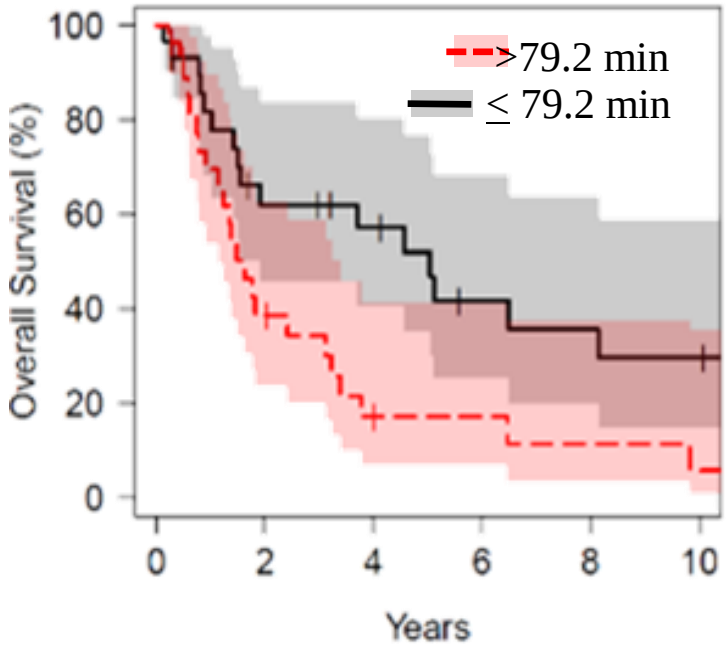


Horsman & Overgaard (1989) In: Hyperthermic Oncology (Urano & Douple, eds.), Vol. 2, pp.113-145.

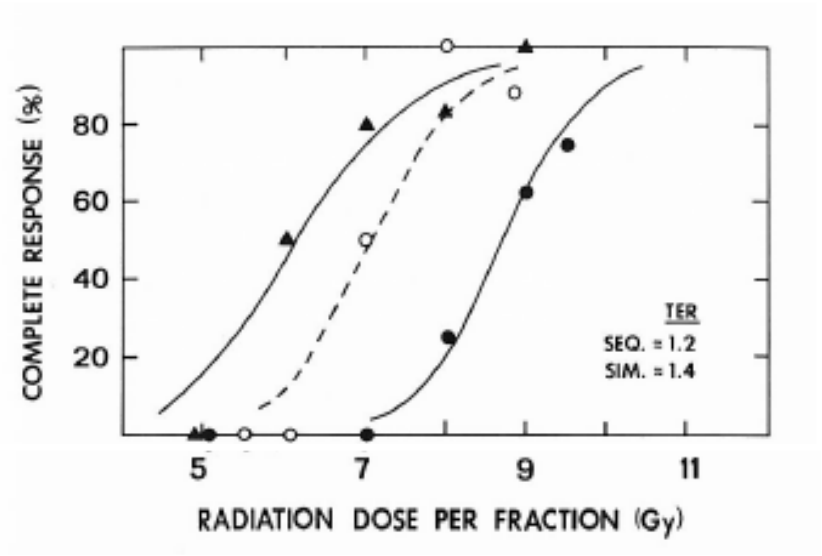
Importance of timing & sequence



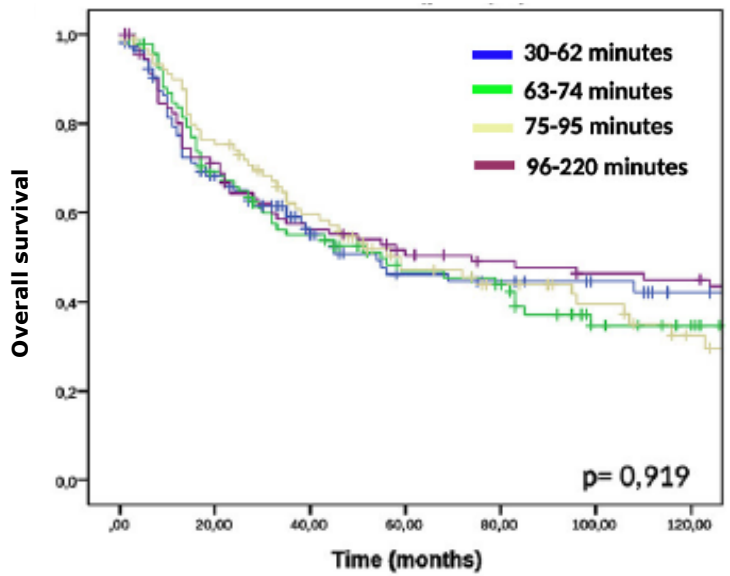
Elming et al. (2019) Cancers



Van Leeuwen et al. (2017) Radiat. Oncol. 12:75



Overgaard & Overgaard (1987) Int J Hyperthermia 3:483-501



Kroesen et al. (2019) Front. Oncol. 9:134

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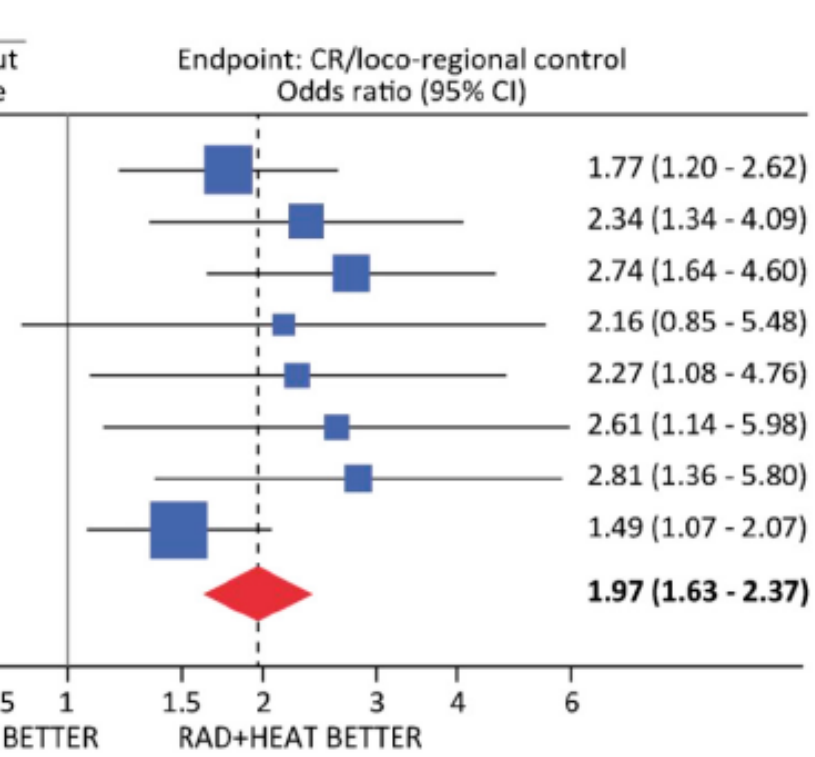
Meta-analysis of randomised clinical trials of radiation (RAD) ± hyperthermia (HEAT)

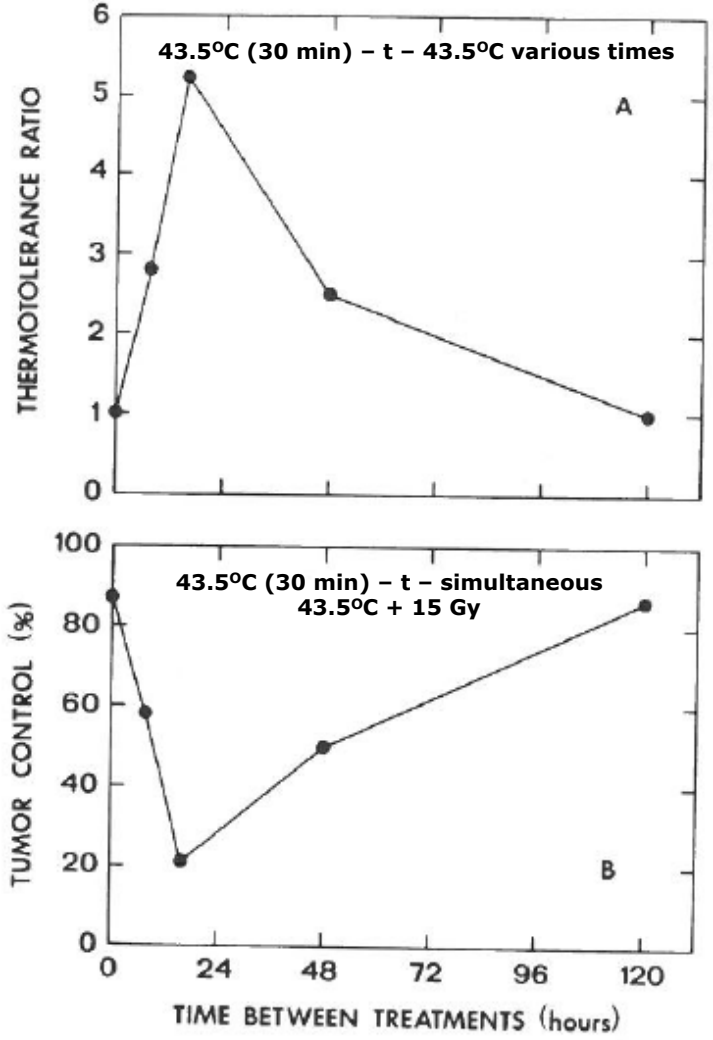
Tumor site	Trials	All pt.	RAD+HEAT Failure	RAD+HEAT All	RAD+HEAT Without failure	RAD ALONE Failure	RAD ALONE All	RAD ALONE Without failure
BREAST	6	419	86	229	62 %	98	190	48 %
HEAD & NECK	4	207	45	104	57 %	66	103	36 %
UTERINE CERVIX	4	249	41	125	67 %	71	124	43 %
LUNG	1	80	11	40	73 %	18	40	55 %
RECTUM	2	258	104	128	19 %	118	130	9 %
BLADDER	1	101	14	52	73 %	24	49	51 %
MELANOMA	1	128	28	63	56 %	45	65	31 %
MIXED	4	610	177	306	42 %	204	304	33 %
OVERALL	**23**	**2052**	**506**	**1047**	**52 %**	**644**	**1005**	**36 %**

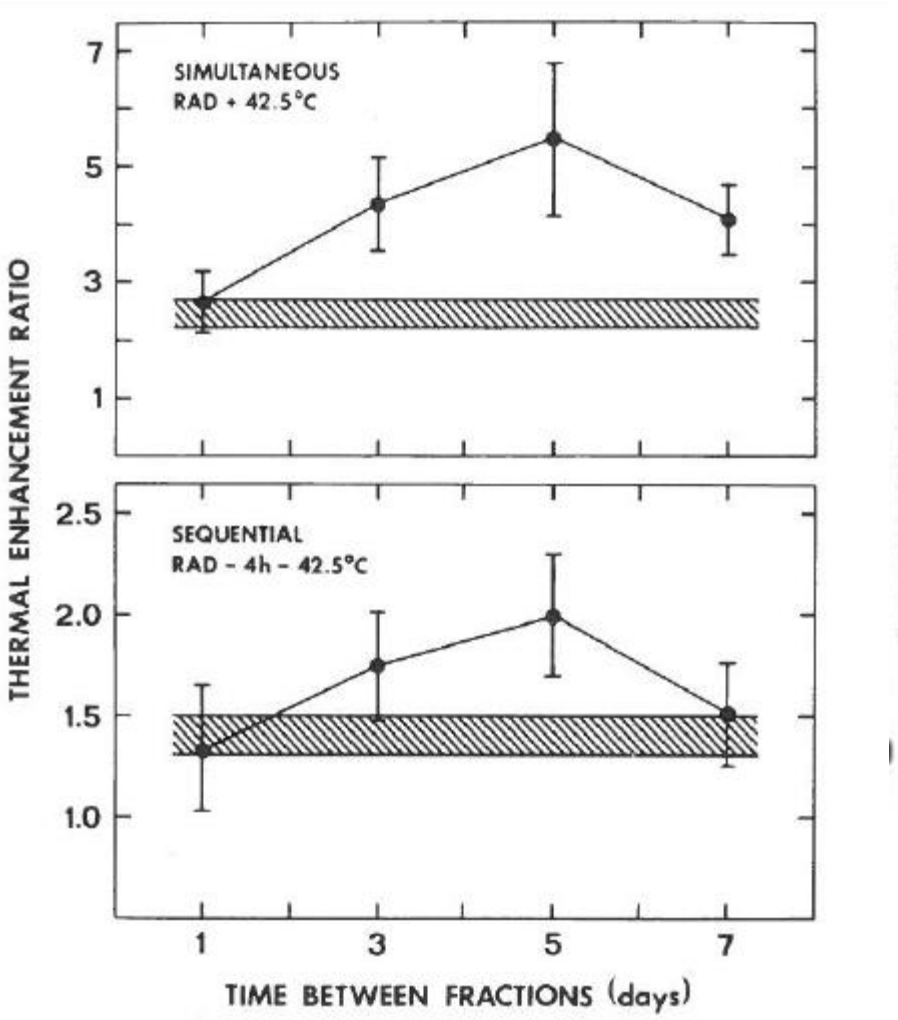
I-squared = 0.0%, p = 0.48



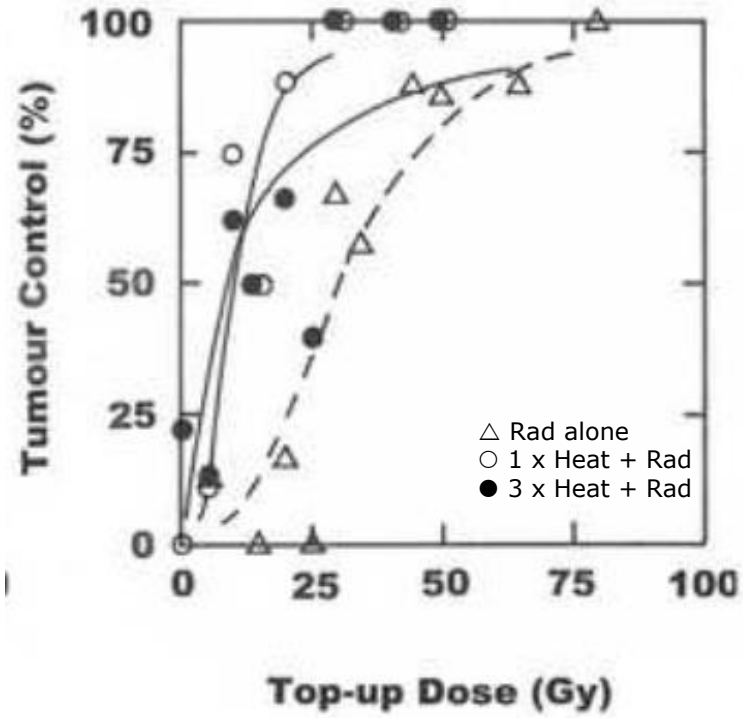
Elming et al. (2019) Cancers

Effect of Thermotolerance on radiation response





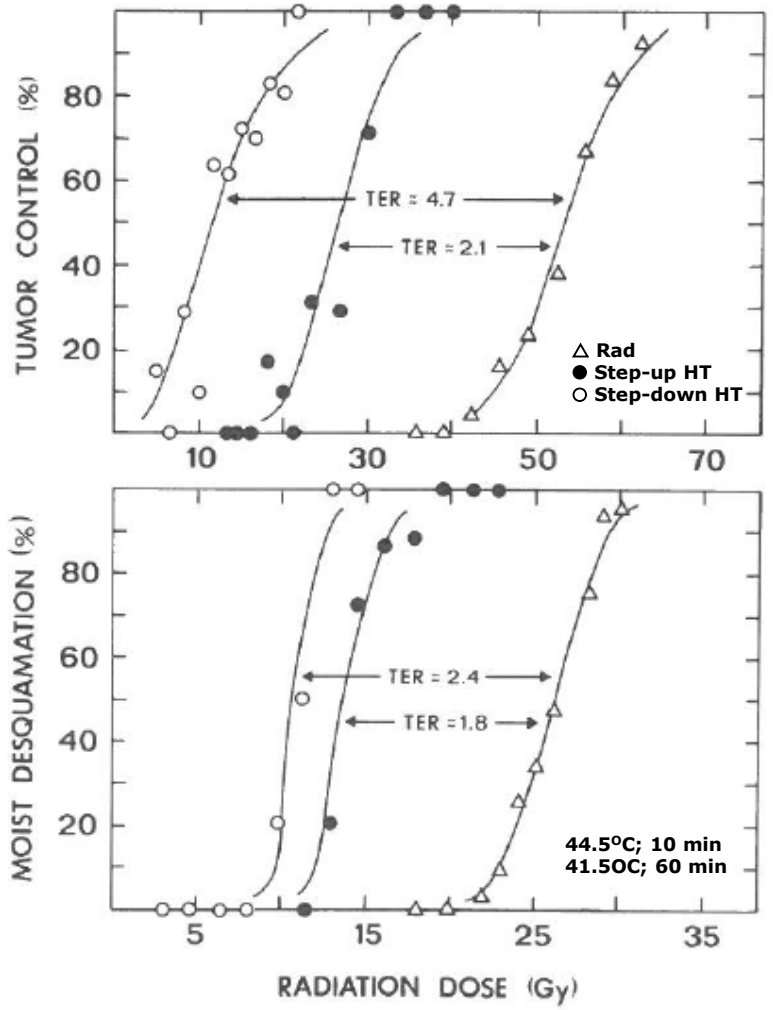
3x15 Gy + Clamped top-up radiation dose

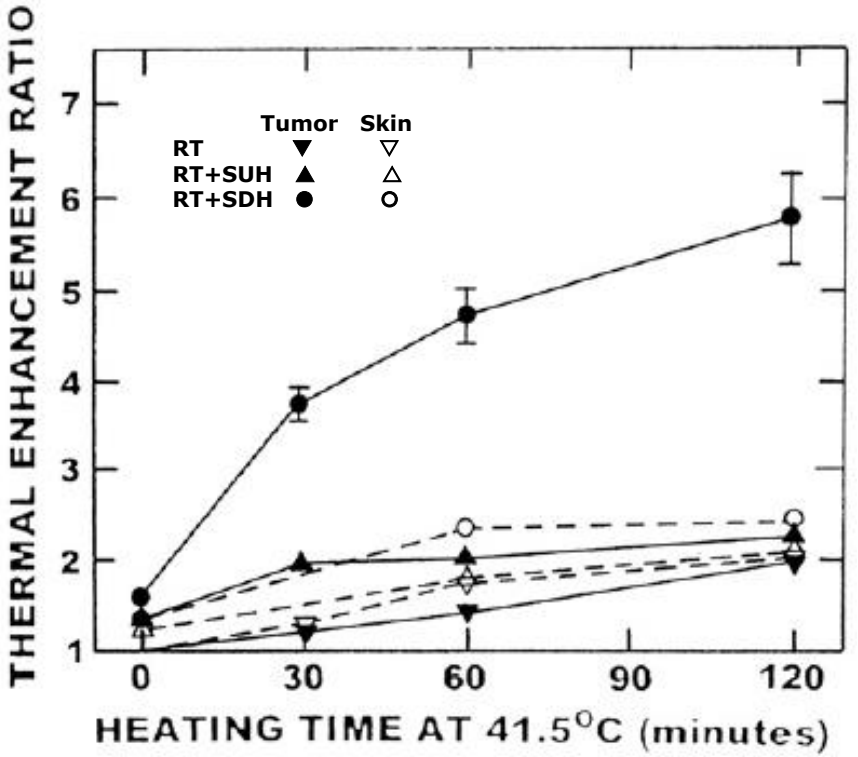


Wittenborn & Horsman (2015) Acta Oncol. 54:1385-1392

Horsman & Overgaard (1989) In: Hyperthermic Oncology (Urano & Douple, eds.), Vol. 2, pp.113-145.

Effect of Step-down (44.5°C-0h-41.5°C) or Step-up heating (41.5°C-0h-44.5°C) on radiation response





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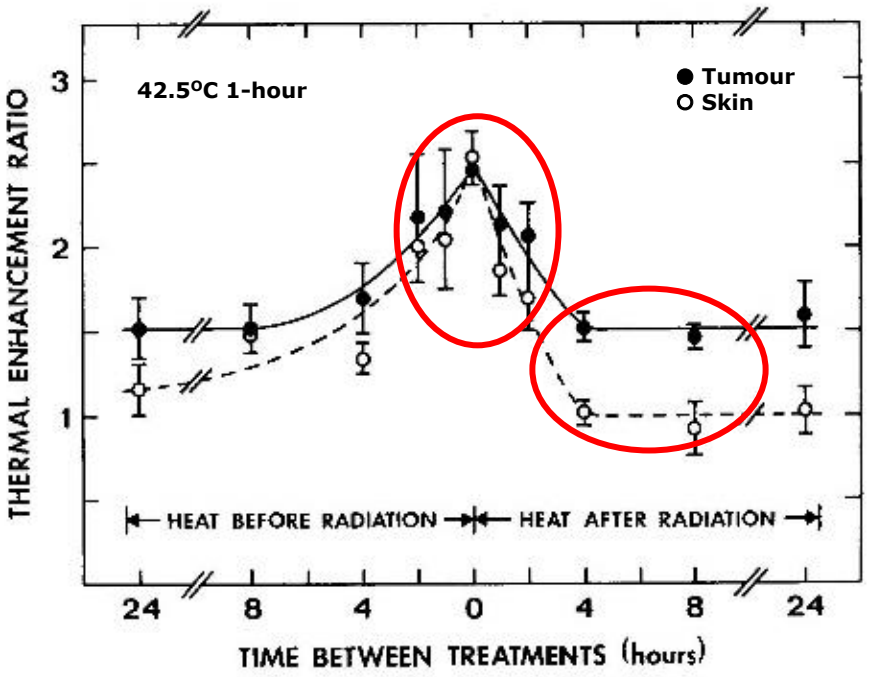
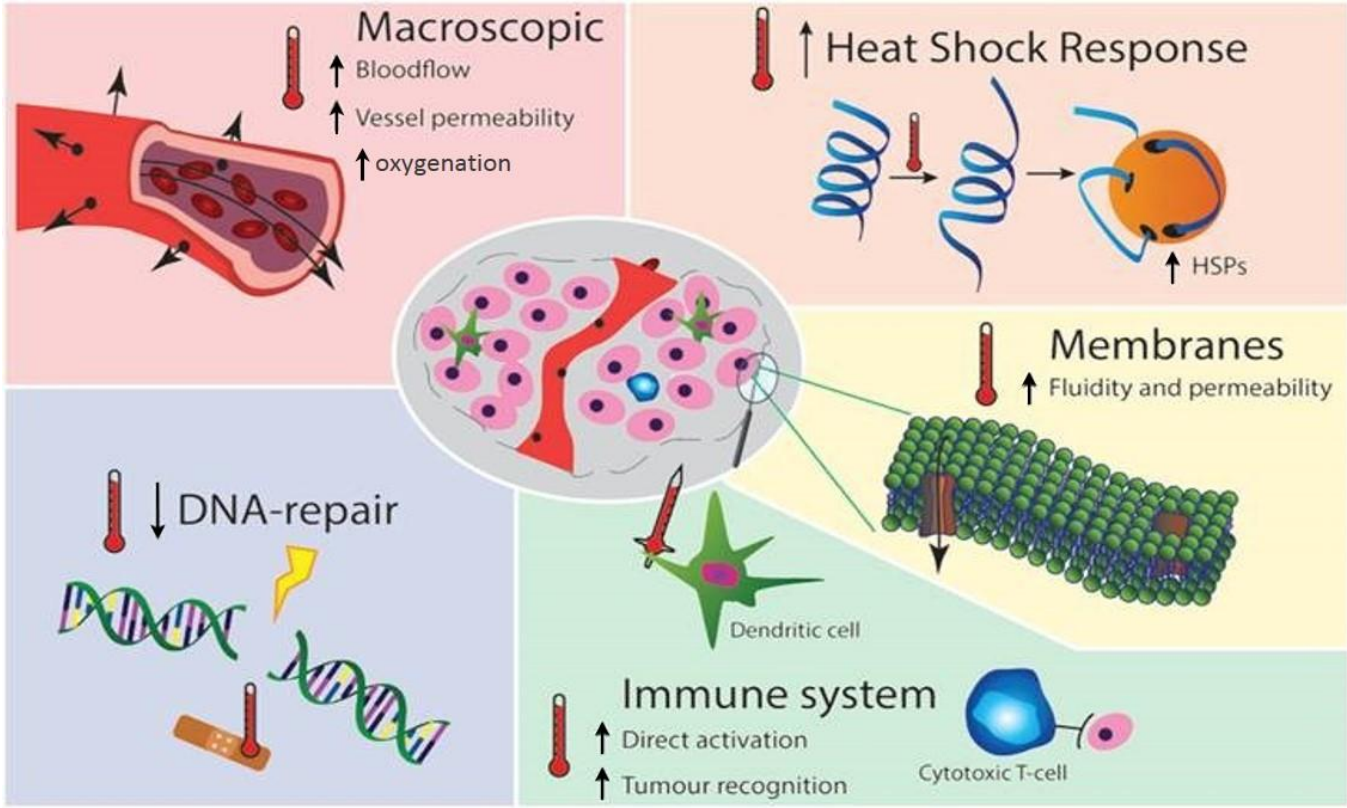
Mechanisms for the interaction between hyperthermia and radiation

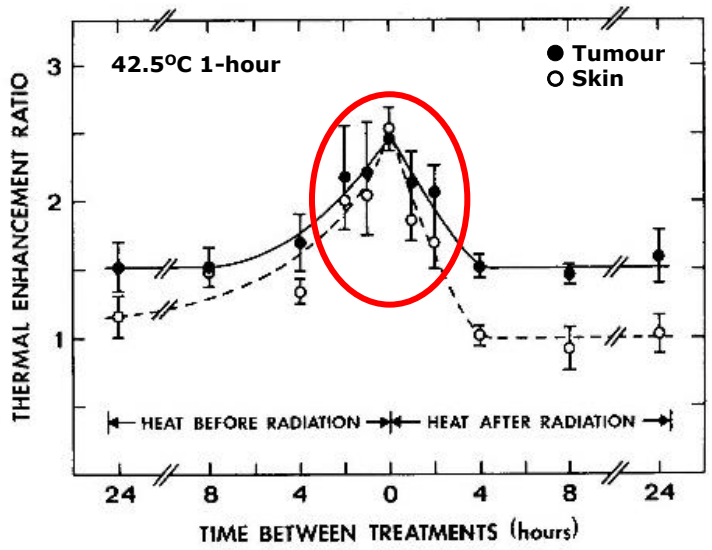


Elming et al. (2019) Cancers



Van den Tempel et al. (2016) Int. J. Hyperther. 32:446-454

DNA repair inhibition



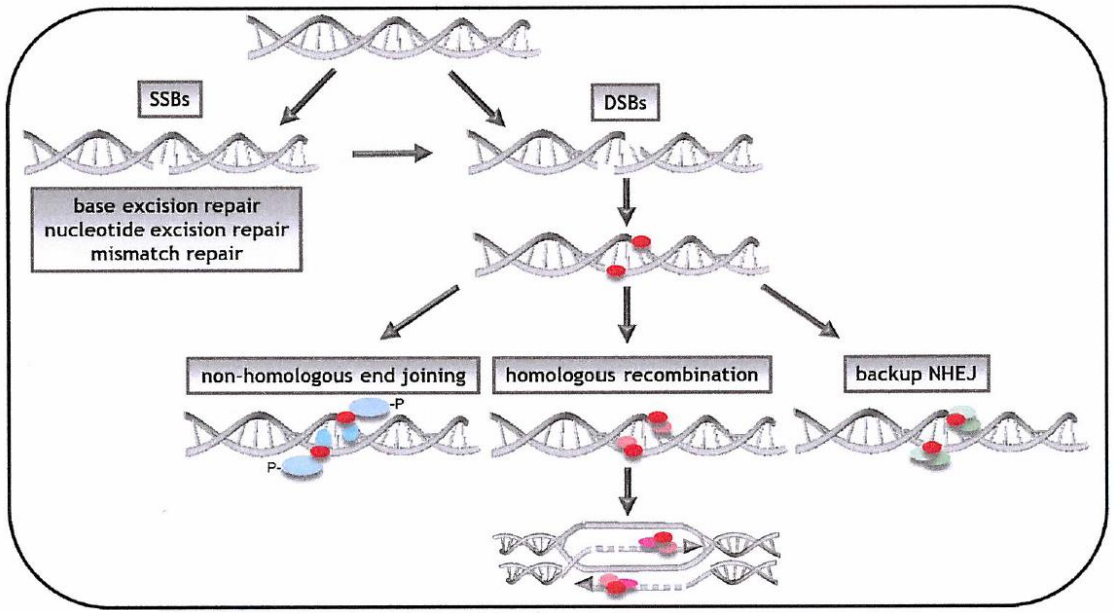


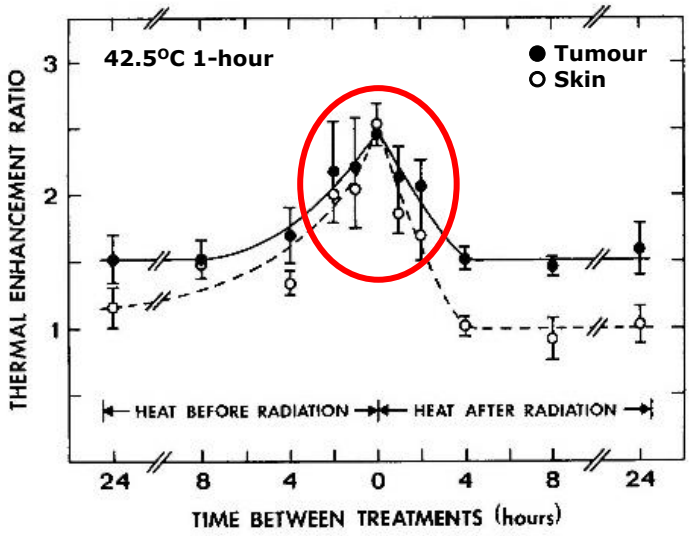
Table 1. DNA repair inhibition by hyperthermia.

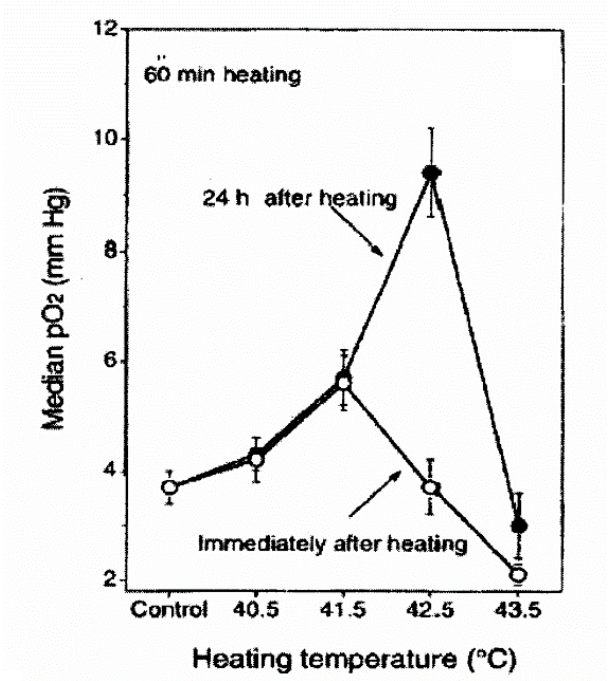
Assay used	Type(s) of DNA damage detected	Inhibition of repair by HT	Temp (°C)	Reference
HPLC	t-type base damage	yes	45	Warters and Roti Roti 1978, 1979
Filter binding assay	DNA–protein crosslinks	yes	43	Cress and Bowden 1983
Alkaline sucrose gradient	strand breaks and alkali labile base damage	yes	⩾ 43	Corry *et al.* (1977), Weniger *et al.* (1979), Kubota *et al.* (1979), Clark *et al.* (1981)
Neutral sucrose gradient	double-strand breaks	yes	43	Corry *et al.* (1977)
Alkaline unwinding	strand breaks and alkali labile base damage	yes	⩾ 42	Dikomey (1982), McGhie *et al.* (1983), Lunec *et al.* (1981), Jorritsma and Konings (1983), Dikomey and Franzke (1992)
Alkaline elution	strand breaks and alakli labile base damage	yes	⩾ 43	Bowden and Kasunic (1981), Mills and Meyn (1981)
Non-denaturing or neutral elution	double-strand breaks and alkali labile base damage	yes	⩾ 43	Radford (1983), Iliakis *et al.* (1990), Warters *et al.* (1987), Warters and Axtell (1992)
Pulsed-field gel electrophoresis	double-strand breaks	yes	⩾ 43	Kampinga *et al.* (1993), Nevaldine *et al.* (1994), Kampinga *et al.* (1997)
Constant-field gel electrophoresis	double-strand breaks	yes	⩾ 43	Dahm-Daphi *et al.* (1997)
Halo assay	strand breaks	yes	45	Kampinga *et al.* (1988), Wynstra *et al.* (1990)
In vitro repair (PFGE)	double-strand breaks	no	45	Wachsberger and Iliakis (2000)

Kampinga & Dikomey (2001) Int. J. Radiat. Biol. 77:399-408

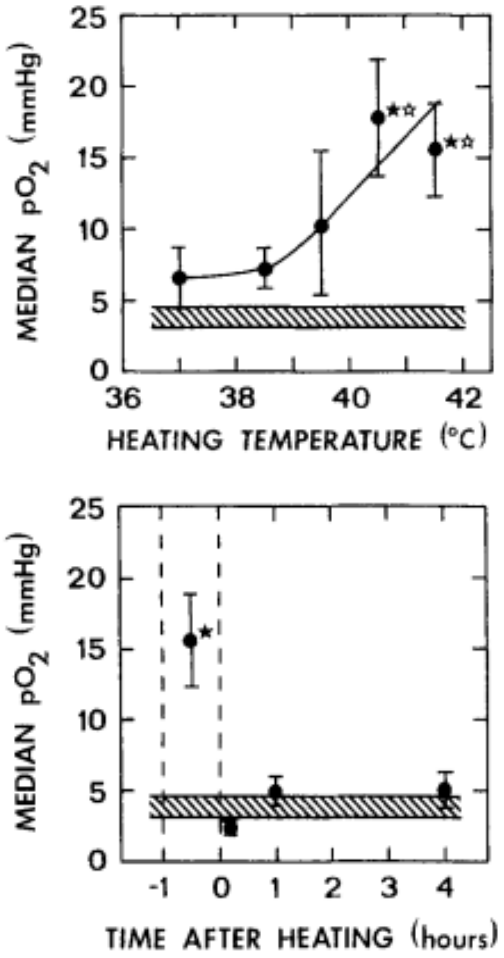
Arlene Oei (personal communication)

Tumor oxygenation

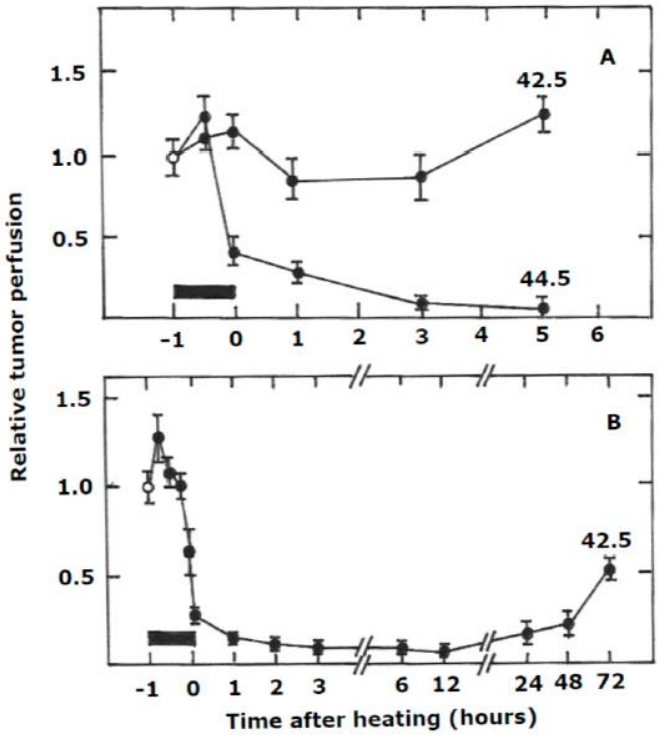




Vujaskovic & Song (2004) Int. J. Hyperthermia 20:163-74

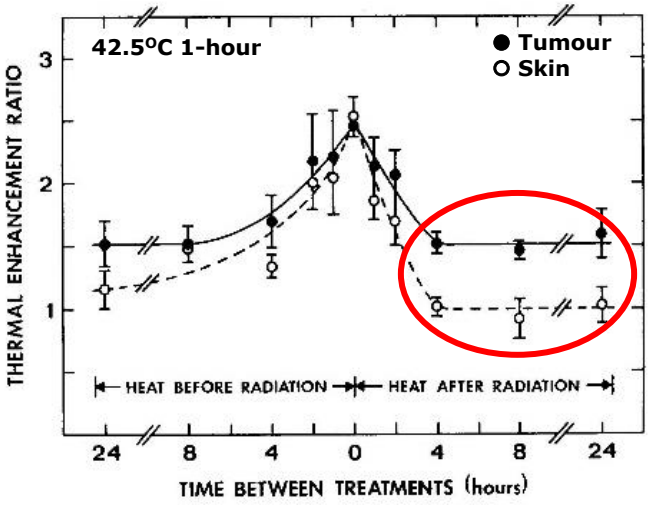


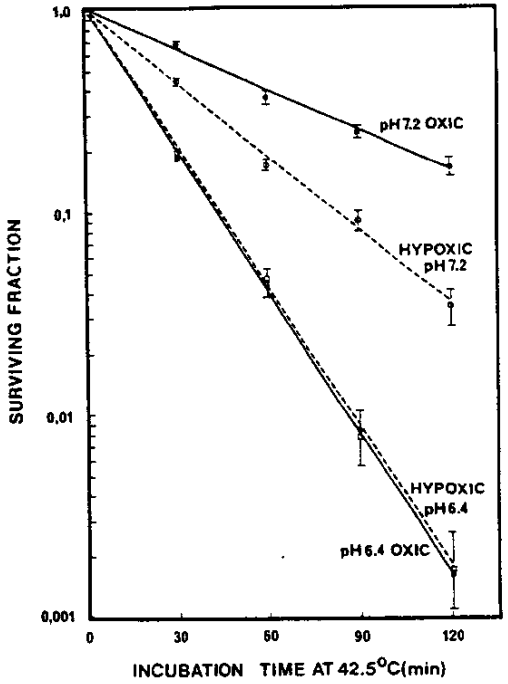
Horsman & Overgaard (1997) Int. J. Hyperthermia 13:141-7



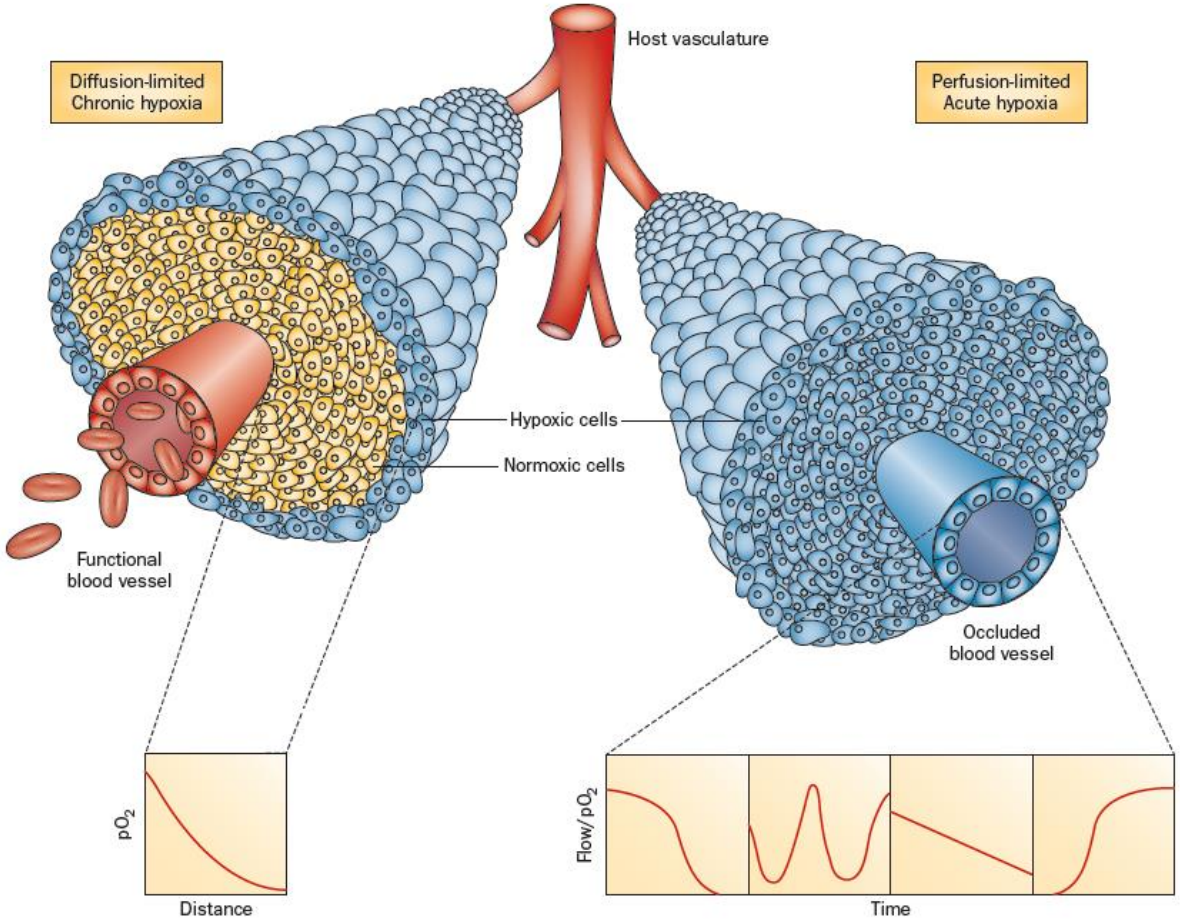
Elming et al. (2019) Cancers

Hypoxia and pH





Overgaard & Bichel (1977) Radiol. 123:511-514



Horsman et al. (2012) Nat. Revs. Clin. Oncol. 9:674-687

HYPERBOOST

Hyperthermia boosting the effect of Radiotherapy

H2020-MSCA-ITN-2020-955625

6 countries
11 beneficiaries
14 PhD students
Budget: € 3,761,881.56

B2 Aarhus University

B1 Amsterdam UMC

B10 EMC Rotterdam

B3 UZH/KSA Aarau

B5 ZHAW Zurich

B7 Medlogix Rome

B9 Chalmers Göteborg

B8 Charité Berlin

B11 MDC Berlin

B4 UKER Erlangen

B6 Sennewald Munich

Project coordination:
Hans Crezee
Amsterdam UMC

AARHUS UNIVERSITY

AARHUS UNIVERSITY HOSPITAL

Conclusions

- **Aim for higher hyperthermia temperatures.**
- **Shorter intervals between radiation & hyperthermia are best.**
- **Do not worry about temperature fluctuations.**
- **One good heating each week is probably sufficient.**
- **The interaction between hyperthermia and protons or hyperthermia and photons appears to be equivalent.**