Biological basis of thermal dose

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- ***Since the early 1900s attempts have been made to find a biological heat dose unit that allows for comparison of the effects of different hyperthermic treatment schedules.***

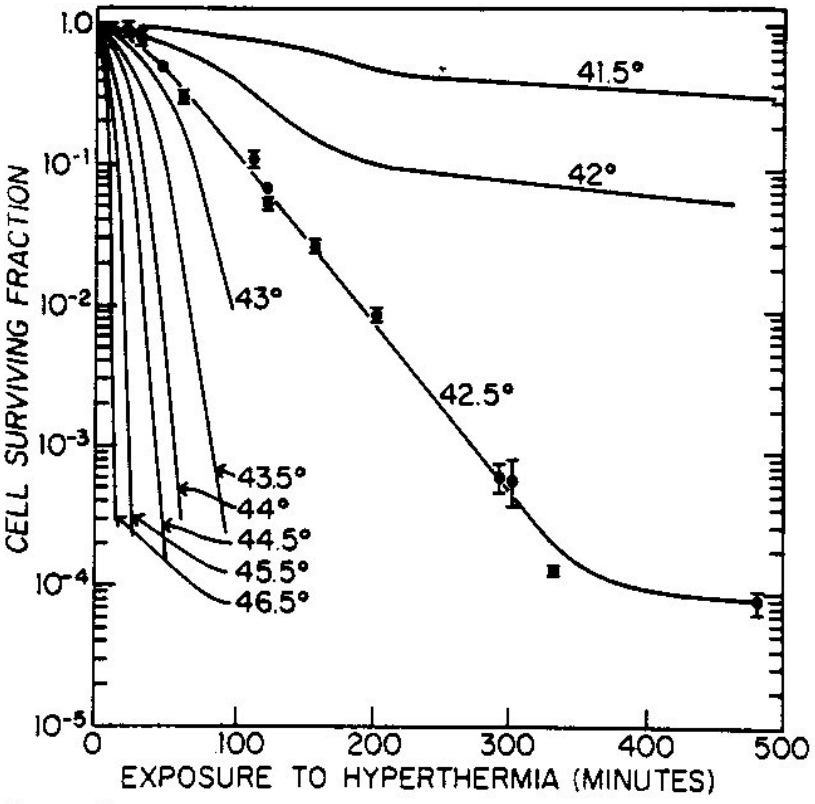
- ***This ultimately led to the concept of converting all thermal exposures to equivalent minutes at a specific temperature.***

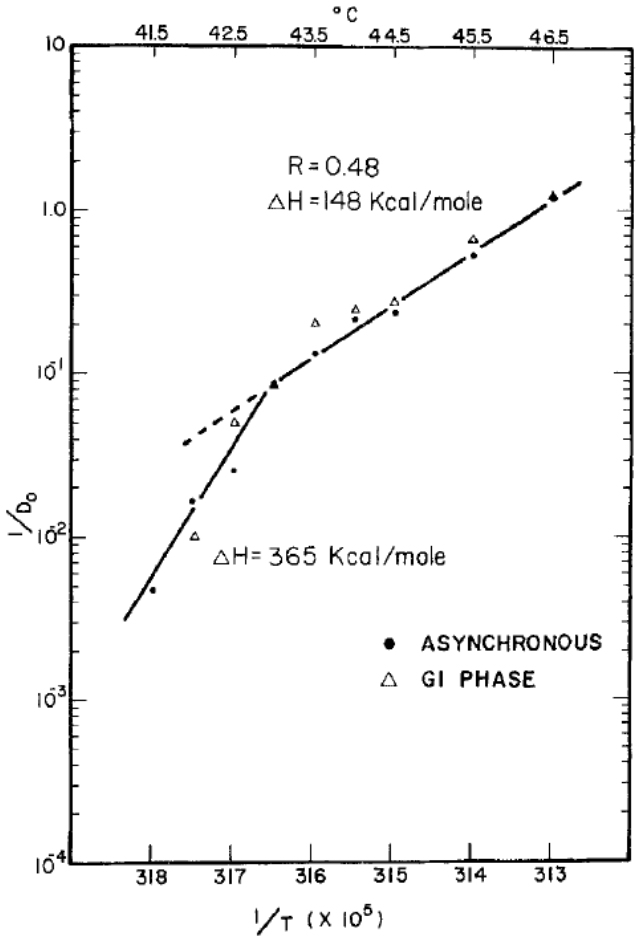
- ***Consequently, Sapareto and Dewey (Int J Radiat Oncol Biol Phys 1984;10:787-800) arbitrarly selected 43^{O}C as the reference temperature.***

- ***It must be remembered that the CEM 43^{O}C (cumulative minutes at 43^{O}C) value does not represent a physical dosimetric quantity and can be influenced by several factors.***

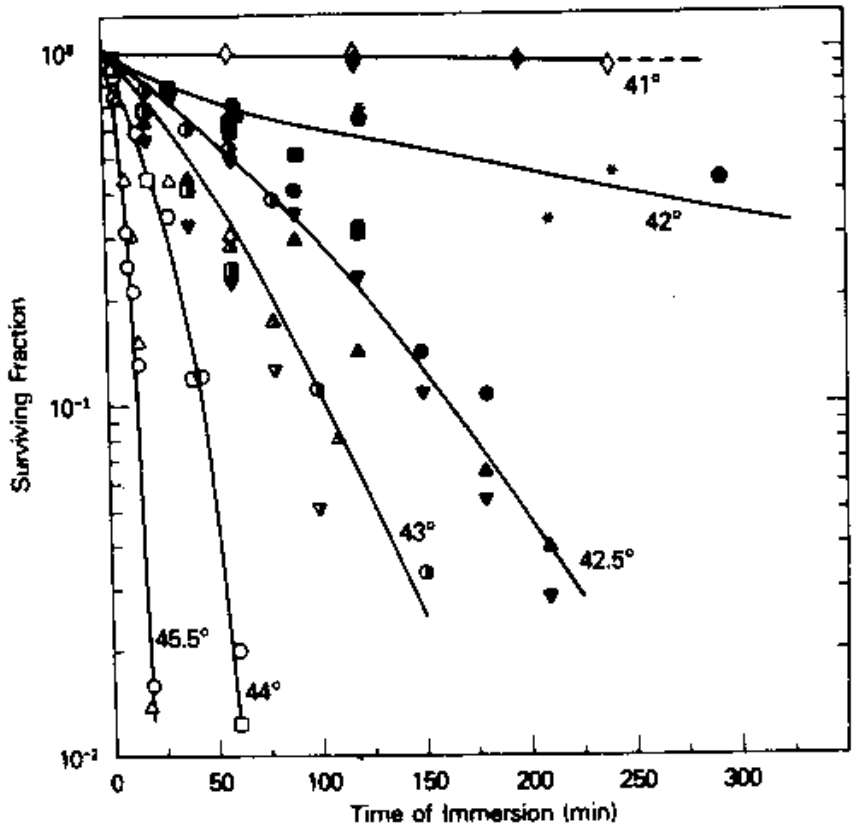
- ***For a good reference on this topic please see Dewhirst et al. (Proc SPIE Int Soc Opt Eng 2003;4954:37).***

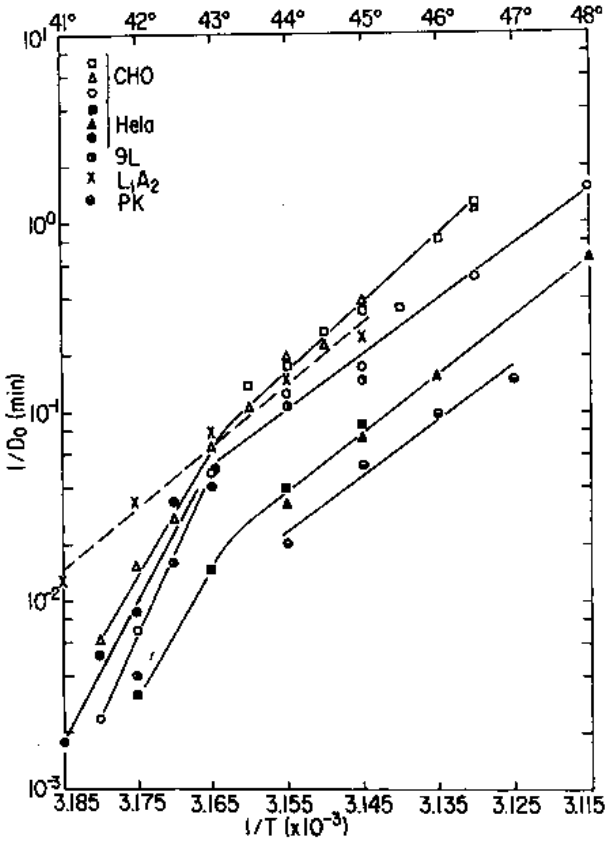
Cell killing by heat



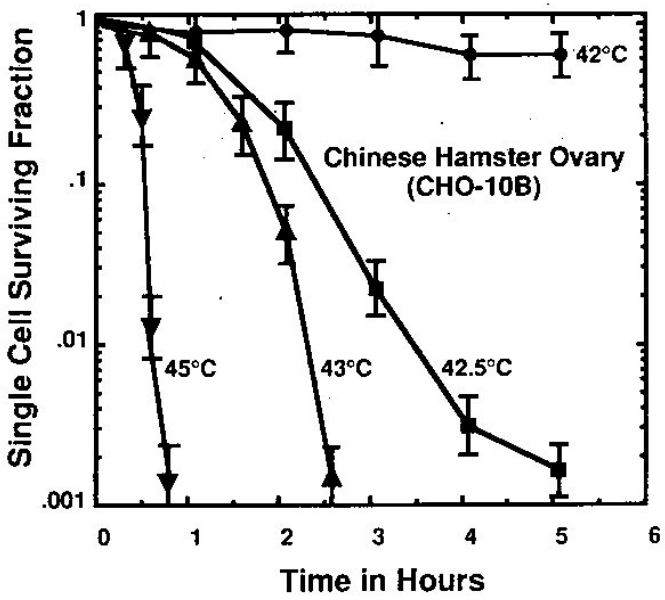


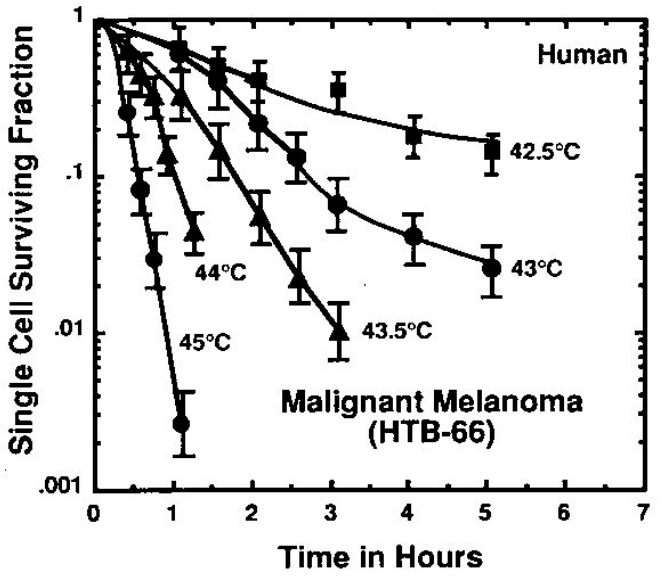
Dewey et al., Radiol (1977) 123:463-474

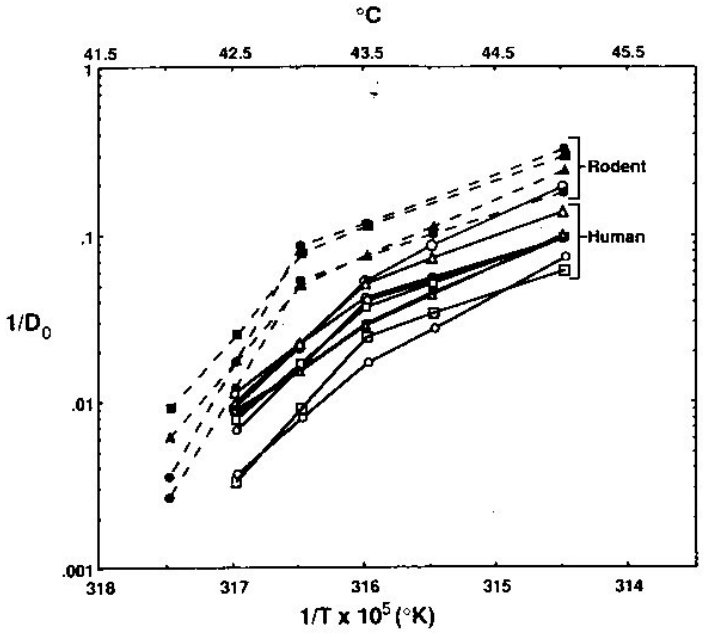




Henle & Roti Roti (1988) Hyperthermia and Oncology 1:57-82

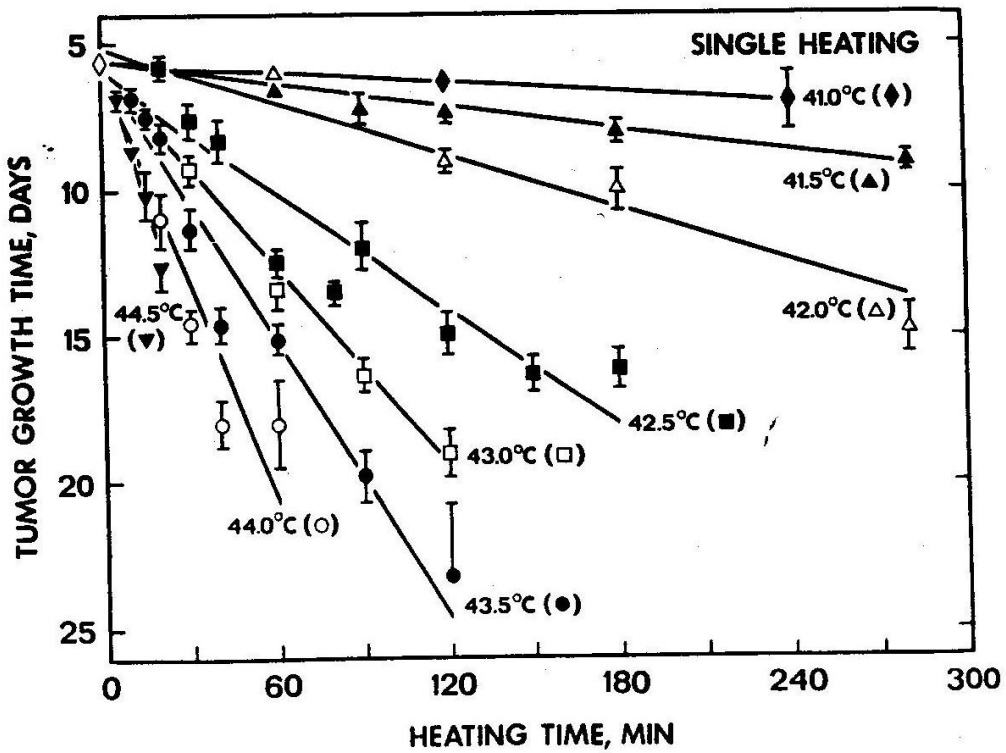


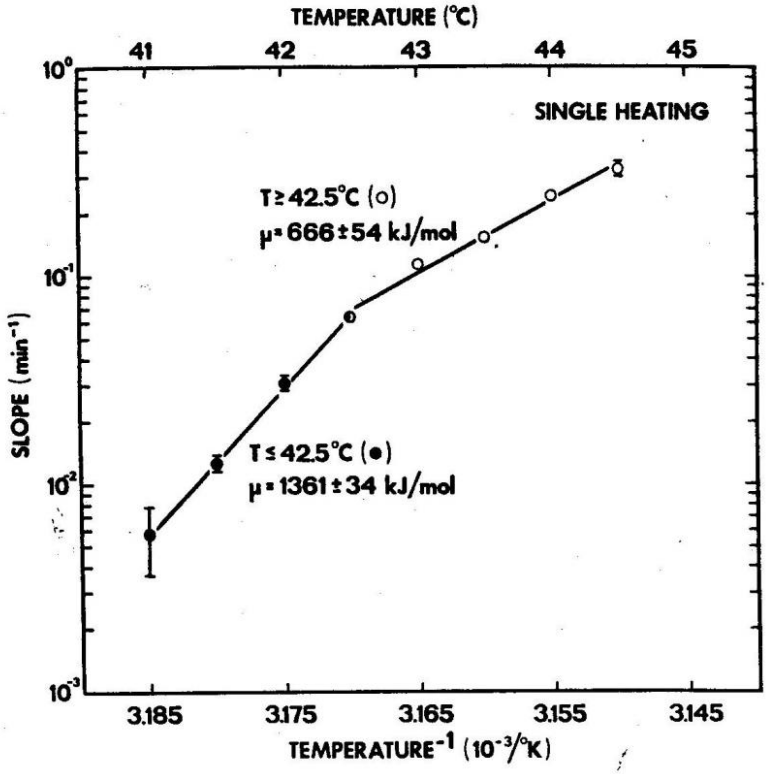




Roizin-Towle & Pirro,
IJROBP (1991) 20:751-756

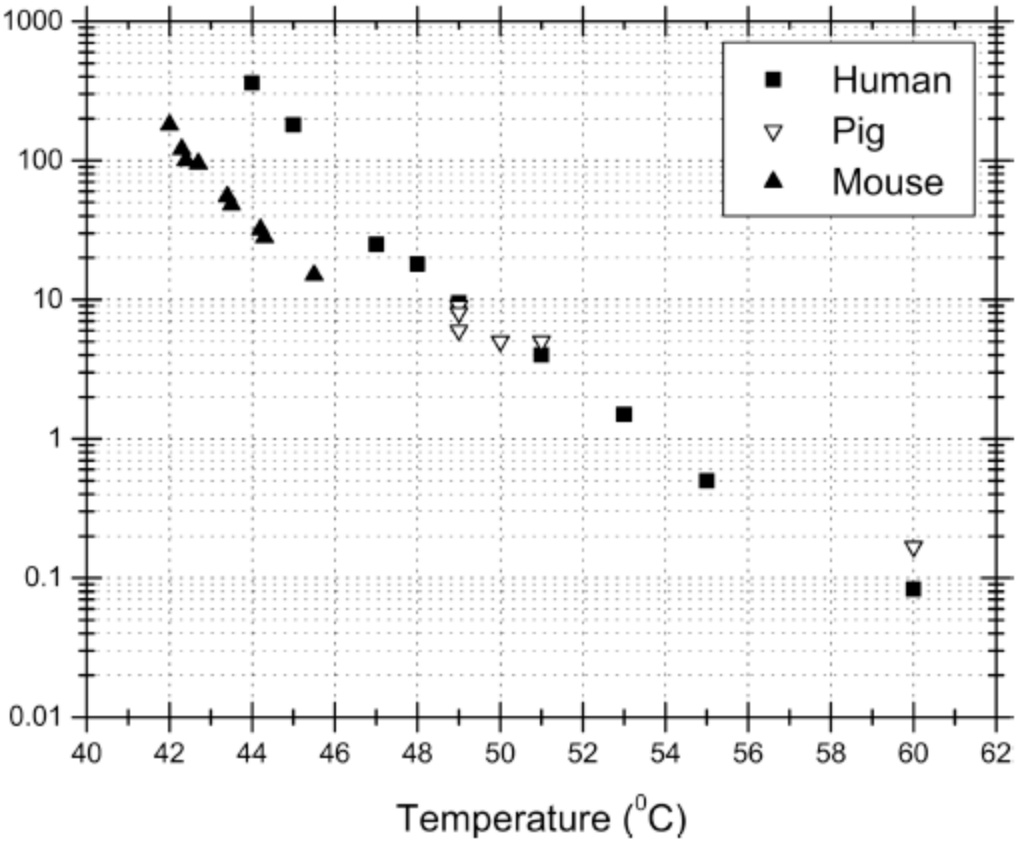
In vivo effects in tumors





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

Time to reach epidermal necrosis as a function of temperature



Species	Temperature Range (°C)	Activation energy (kcal/mole
Man	44 – 47 / 47 – 60	182.2 / 95.78
Pig	44 – 47 / 48 – 56	150.75 / 106.38
Mouse	41.5 – 42.5	273.89

Dewhirst et al. (2003) Proc SPIE Int Soc Opt Eng 4954:37

Table 1.
Time–temperature relationships for thermal injury in normal tissues

Tissue	Endpoint	Temperature range (°C)	Transition temperature °C	Time factor for 1 °C		Temperature for 60 minutes °C	Authors
				Below 42.5 °C	Above 42.5 °C		
Testis of mouse	50 per cent weight loss	39.5–43.8	No transition	–	2.2	41.3	Hand *et al.* (1979)
Jejunum of mouse	50 per cent crypt loss	42.0–44.5	42.3	8	2.2	42.4	Hume *et al.* (1979a)
Jejunum of mouse	LD_{50}	43.0–46.0			2.0	42.4	Henle (1982)
Jejunum of hamster	LD_{50}	42.5–44.5			2.0	43.3	Milligan *et al.* (1984)
Tail of baby rat	Stunting in 5 per cent	42.0–46.0			2.0	43.3	Morris *et al.* (1977)
Pinna of mouse	Necrosis in 50 per cent	41.5–45.5	42.1	6	2.0	43.3	Law *et al.* (1978)
Skin of rat	Delay of hair growth	42.0–46.0			1.8	43.4	Okumura and Reinhold (1978)
Tail of baby rat	Necrosis in 50 per cent	41.8–46.0	42.8	6	1.8	43.4	Field and Morris (1983)
Foot of mouse	Loss of toe in 50 per cent	42.5–45.5			2.2	43.6	Overgaard and Suit (1979)
Foot of mouse	Loss of toe in 50 per cent	41.5–46.5	42.5	5	1.9	44.8	Urano *et al.* (1984)
Foot of mouse	Skin response in 50 per cent	43.5–45.0			2.0	44.8	Robinson *et al.* (1978)
Foot of mouse	Loss of feet in 50 per cent	43.0–49.0			2.0	45.7	Crile (1963)
Skin of pig and man	Threshold for necrosis	44.0–55.0			2.2	46.5	Moritz and Henriques (1947)

Law (1988) Hyperthermia & Oncology 1:121-159

Potential poblems with a heat dose concept in the clinic

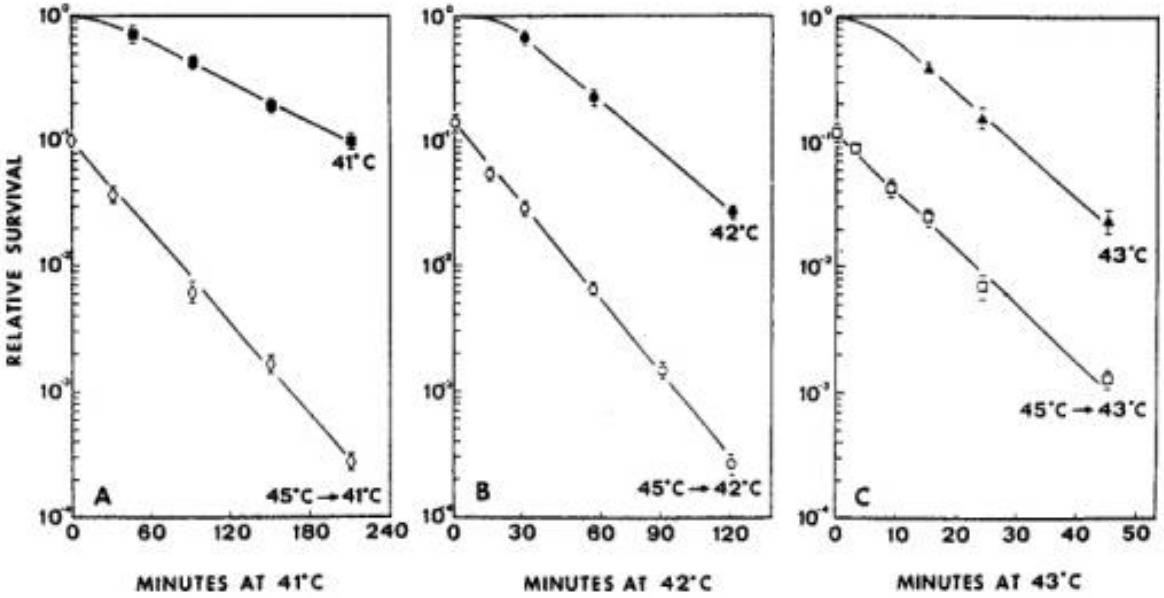
- ***The heat distribution in a tumor is heterogeneous and a uniform temperature distribution is not likely to exist.***

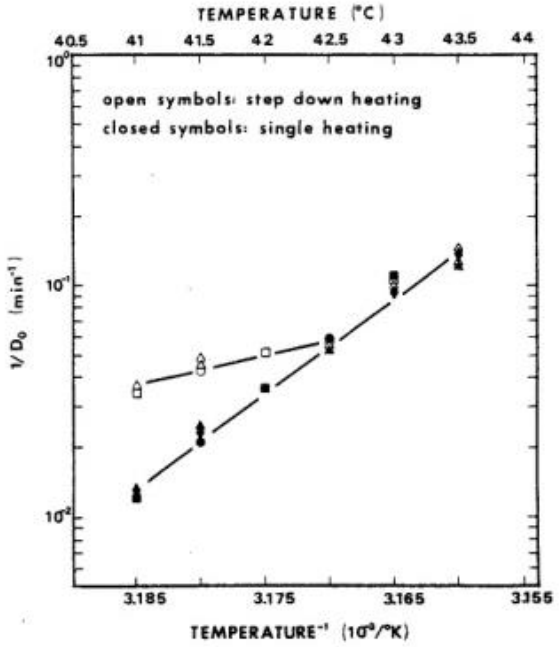
- ***These temperature variations are hard to monitor and may fluctuate (i.e., step up/step-down heating).***

- ***Most clinical treatments are given in fractionated schedules and thermotolerance may influence the biological heat effect at some point.***

- ***Therapeutic hyperthermia involves combination with conventional treatments (i.e., chemotherapy or radiation) and the time-temperature relationships may be different from that seen for heat alone.***

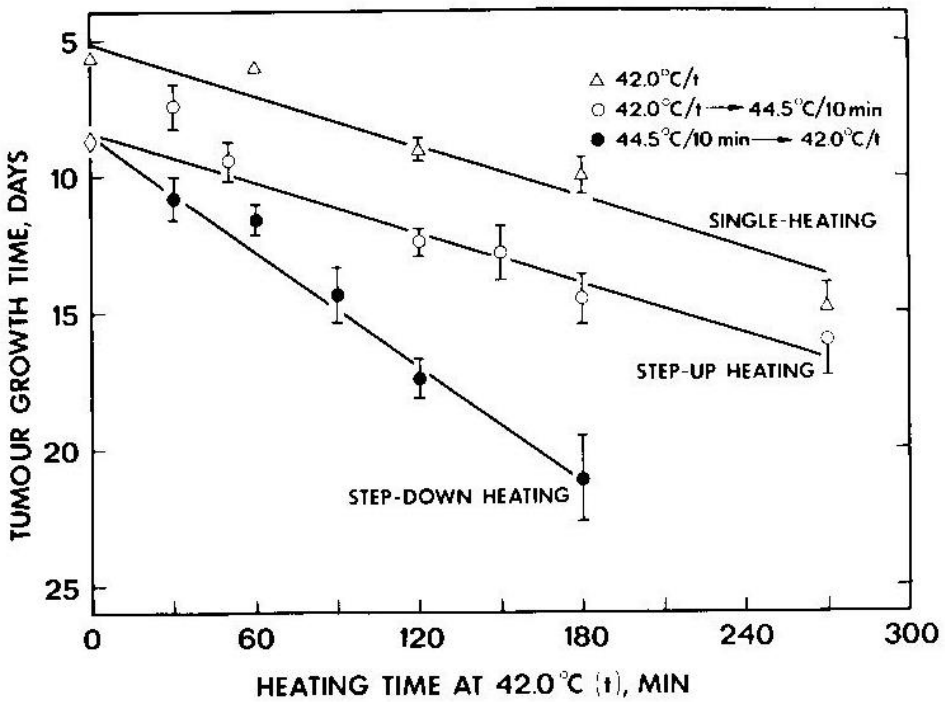
Step-up/Step-down heating in vitro

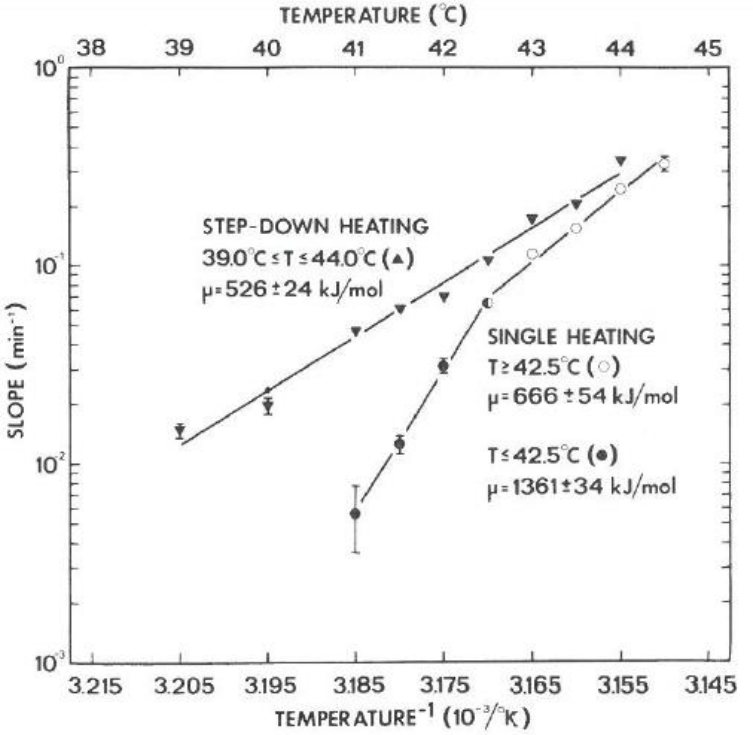




Nielsen et al. (1982) Radiat. Res. 91:468-482

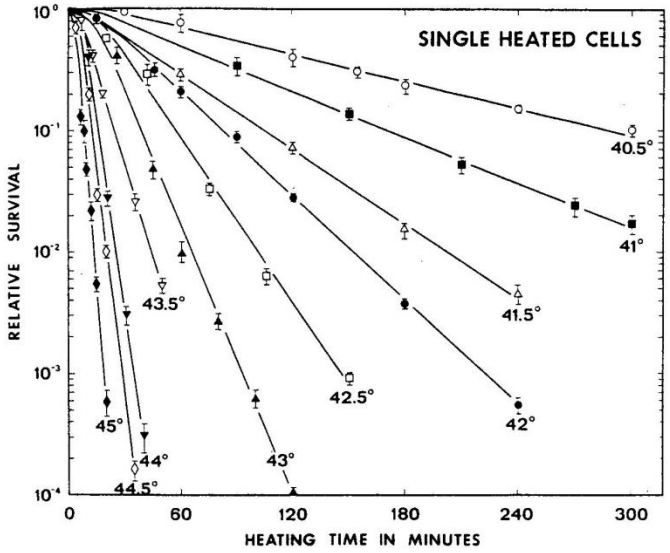
Step-up/Step-down heating in vivo

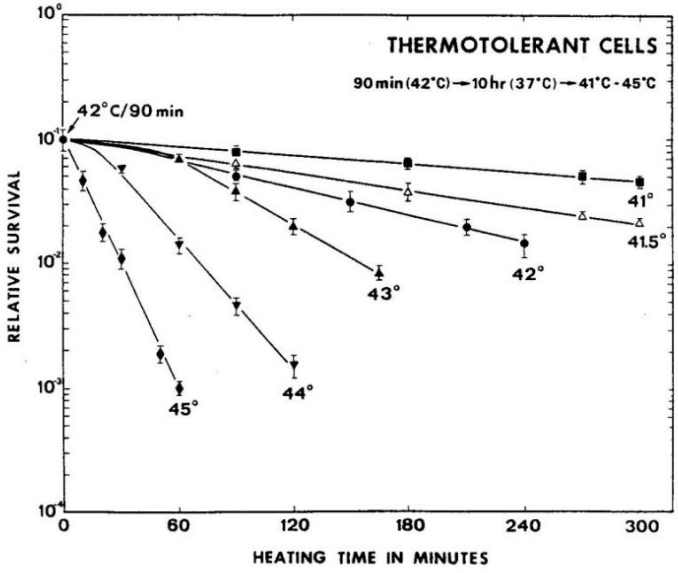


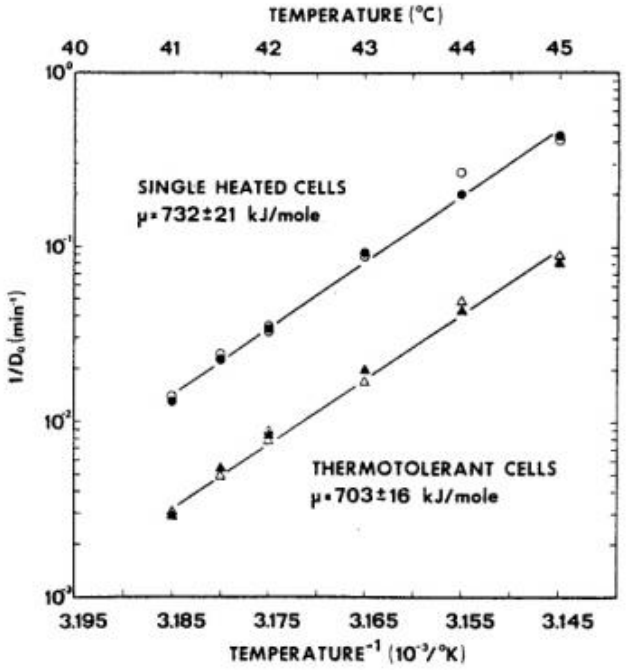


Lindegaard & Overgaard (1987)
Int. J. Hyperthermia 3:79-81

Thermotolerance in vitro

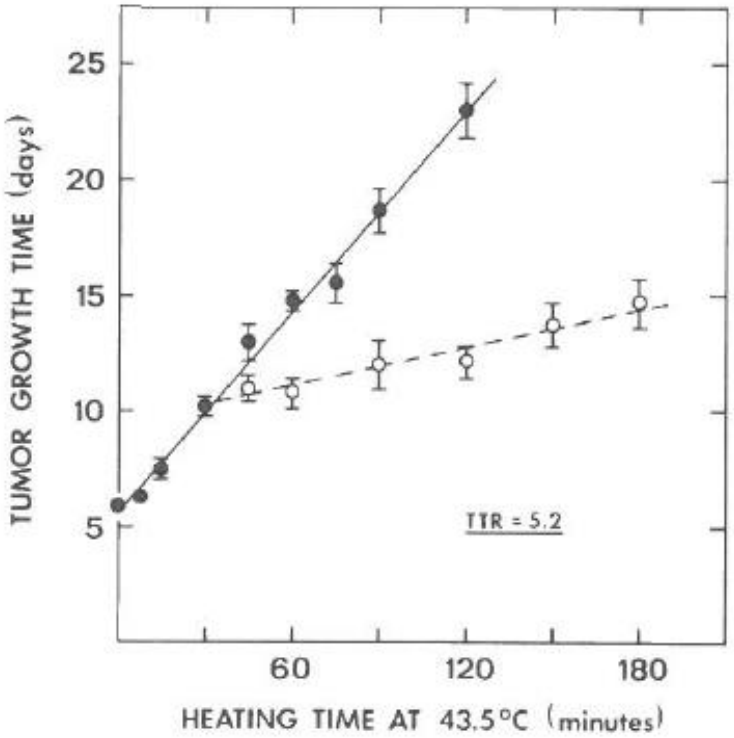


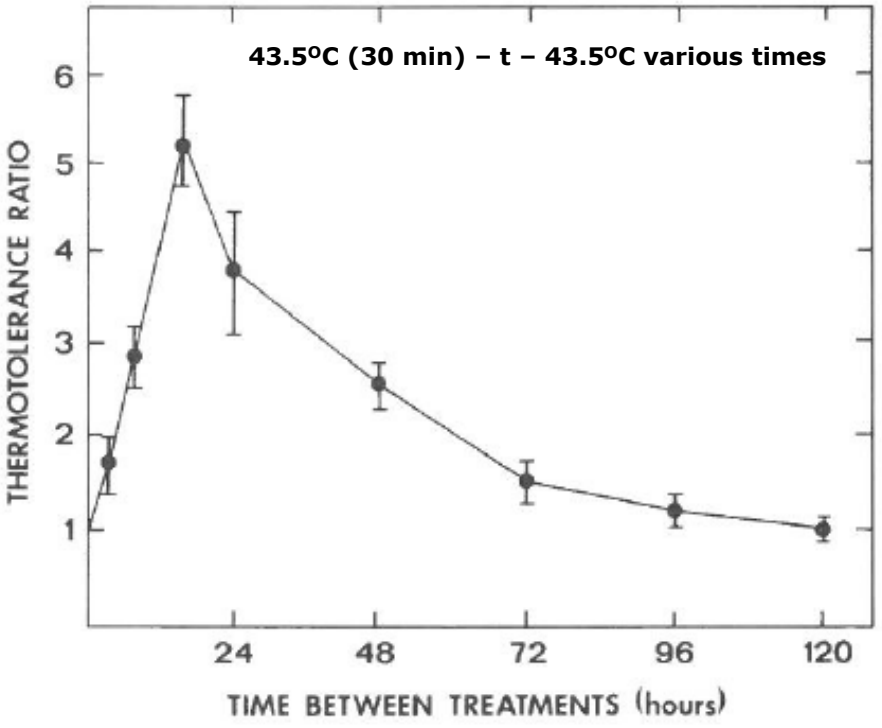




Nielsen et al. (1982) Radiat. Res. 91:468-482

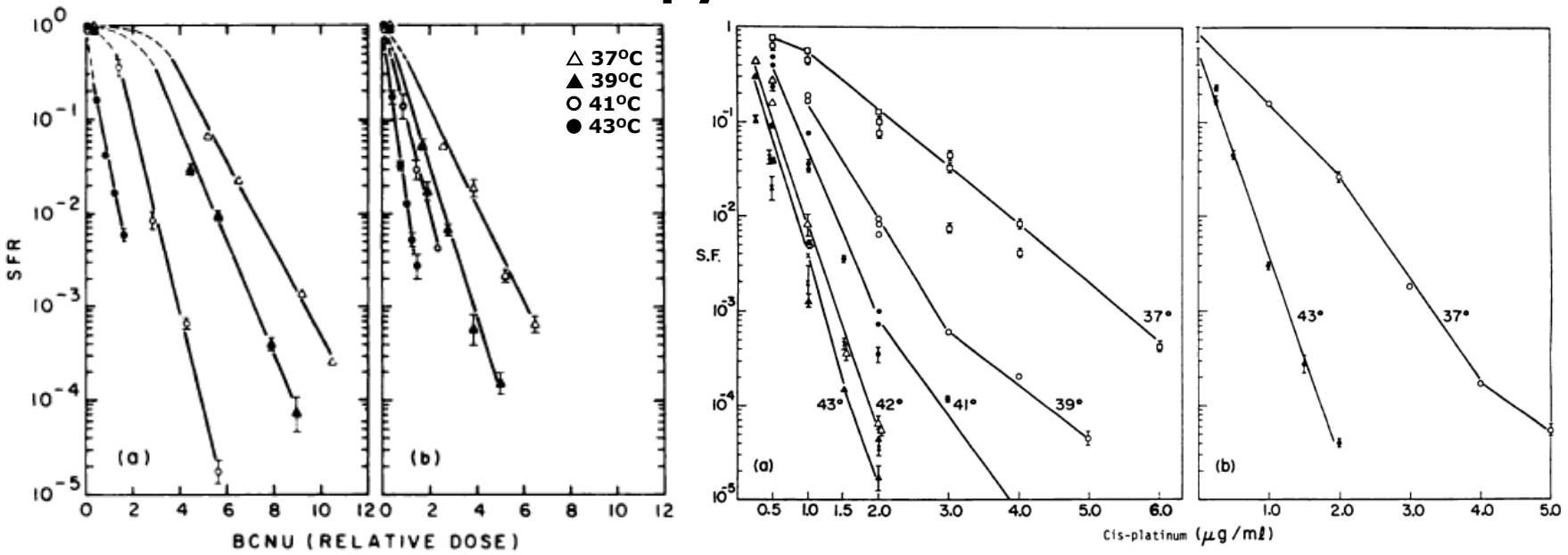
Thermotolerance in vivo





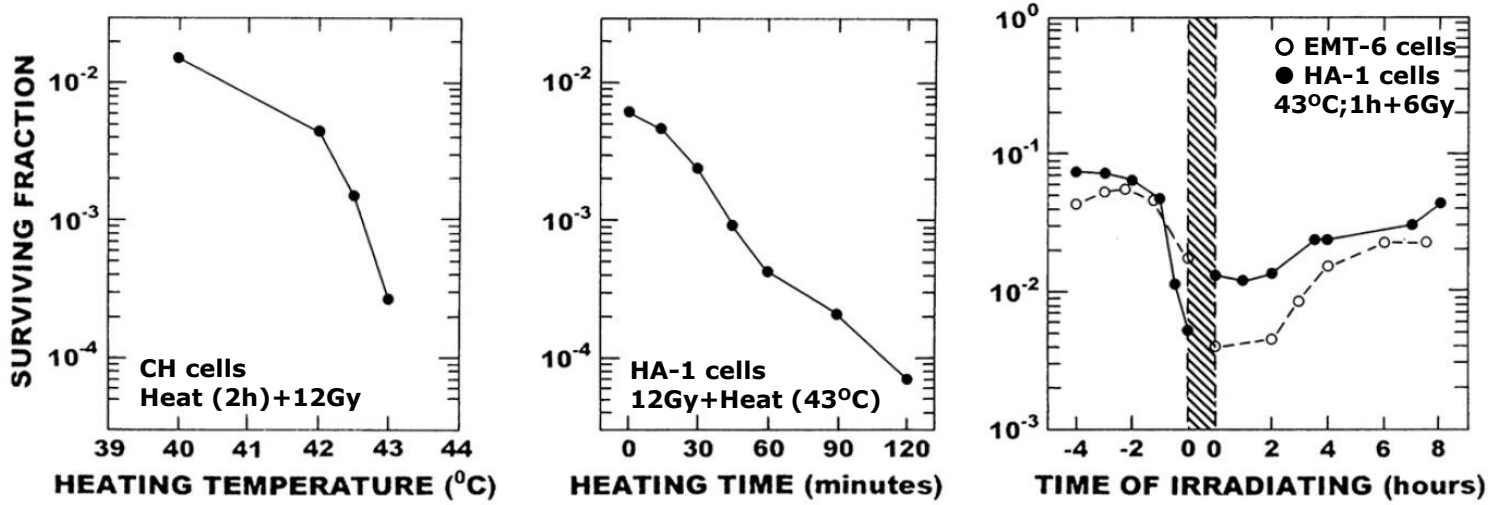
Horsman & Overgaard (1989) In: Hyperthermic Oncology (Urano & Douple, eds.), Vol. 2, pp.113-145.

Chemotherapy and Heat in vitro



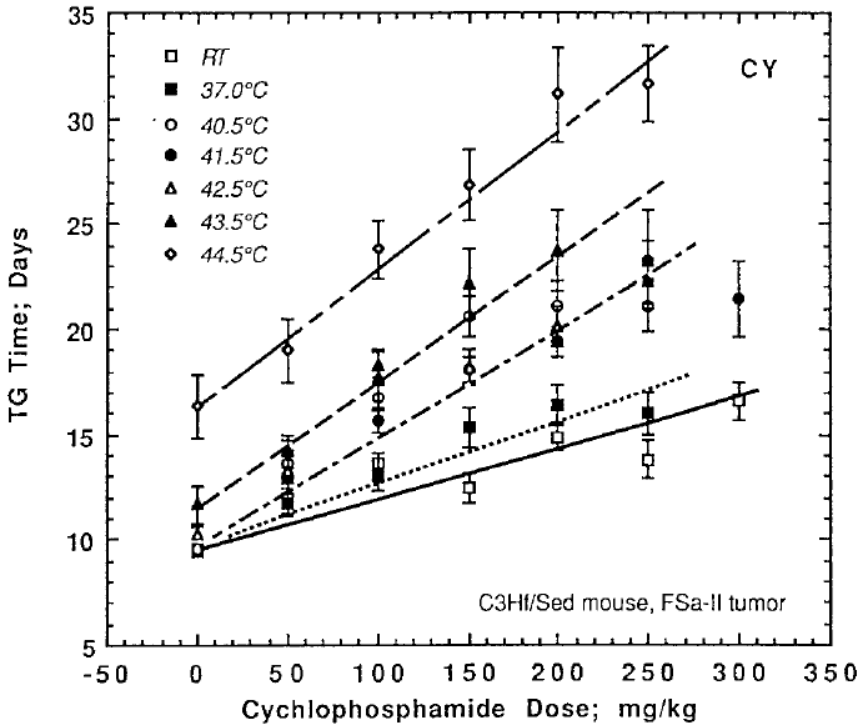
Hahn (1979) Cancer Res. 39:2264-2268

Radiation and Heat in vitro



Horsman & Overgaard (2007) Clin. Oncol. 19:418-426

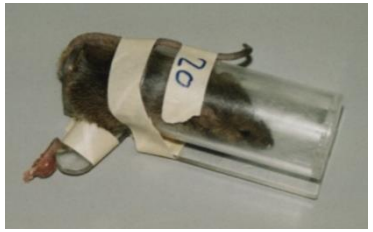
Chemotherapy and Heat in vivo

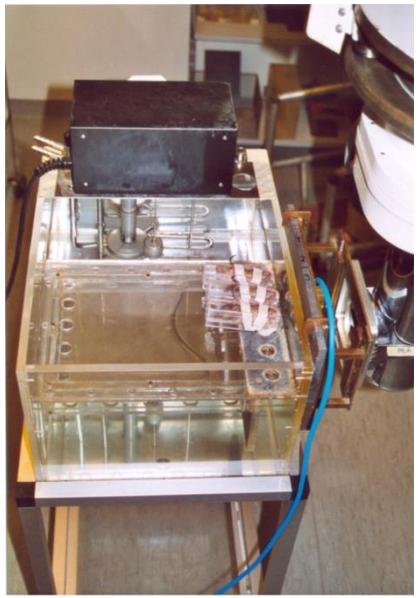


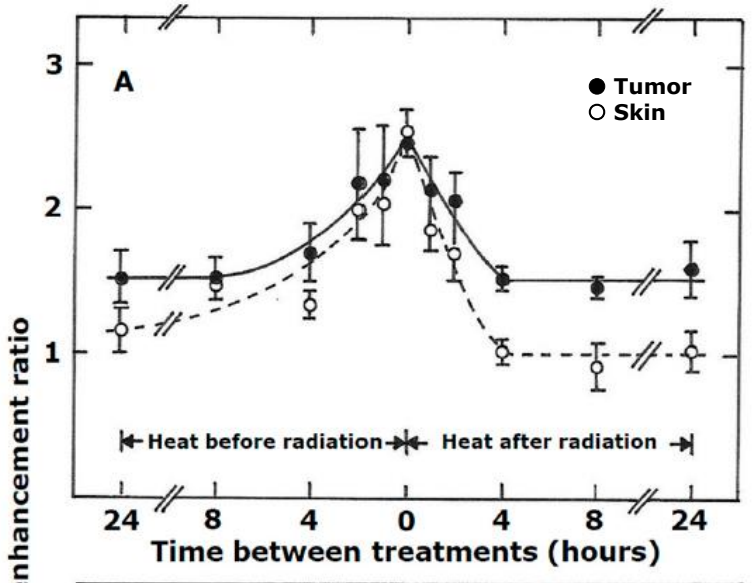
Drug	Treatment Time (min)	TER 41.5°C	TER 43.5°C
5-Fluorouracil	30	1.0	1.0
Adriamycin	30	1.0	1.0
Mitomycin C	30	1.05	---
Bleomycin	30	1.24	1.65
Cisplatin	30	1.48	1.59
Ifosphamide	30	1.52	---
	90	3.60	---
BCNU	30	2.27	2.72
Cyclophosphamide	30	2.28	2.74
Melphalan	30	3.60	---

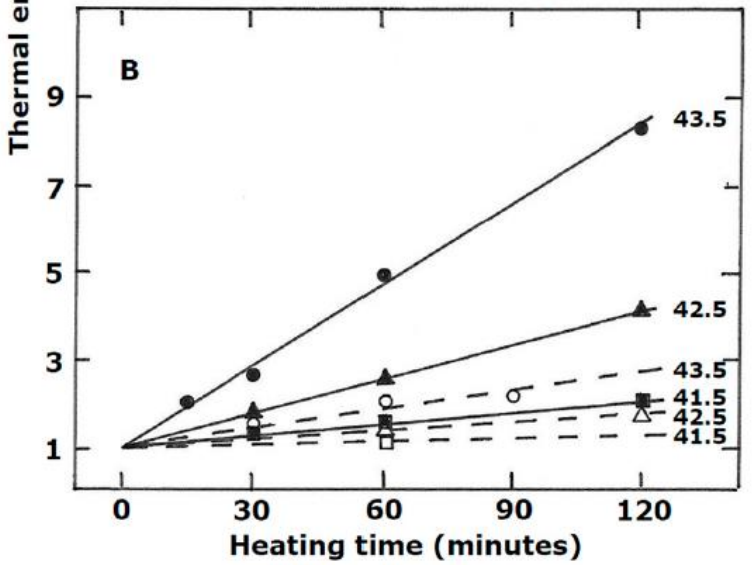
Urano et al. (1999) Int. J. Hyperthermia 15:79-107

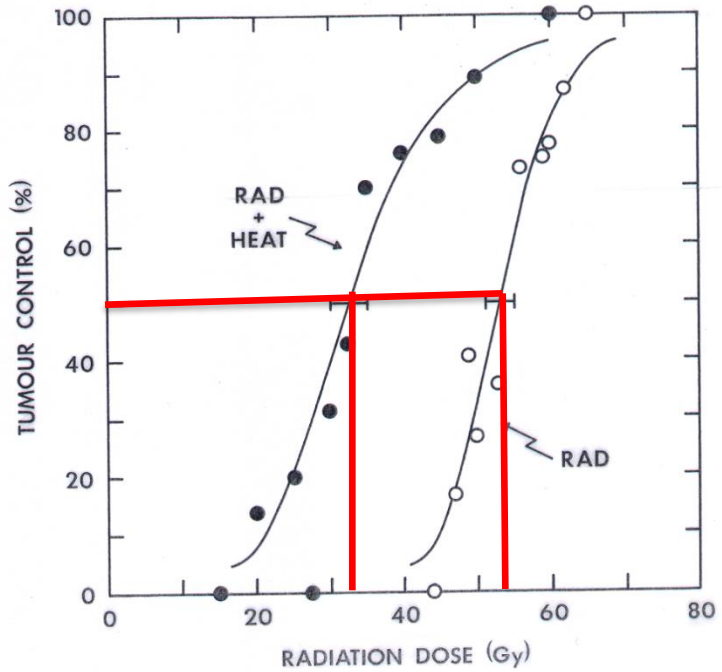
Radiation and Heat in vivo



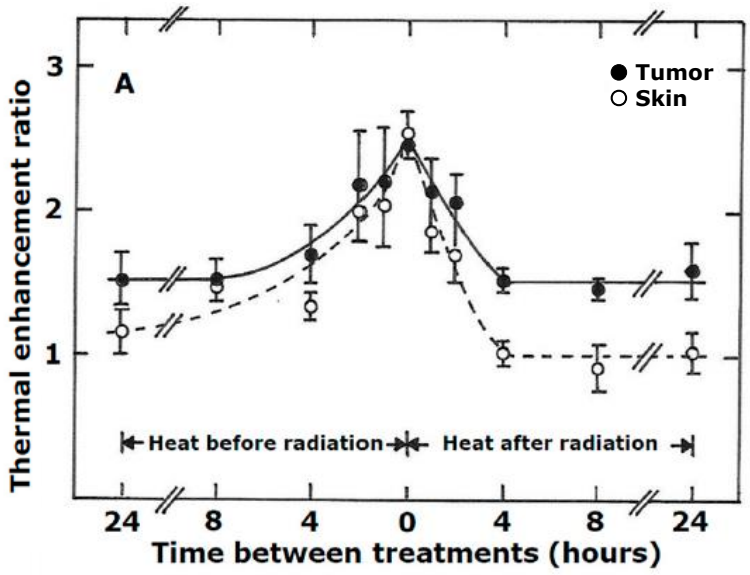


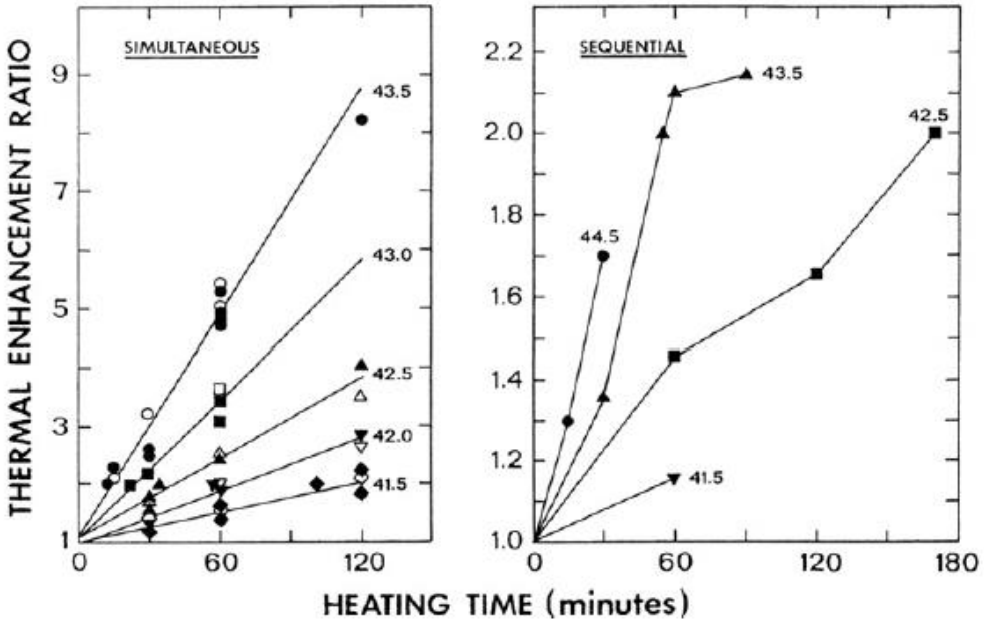


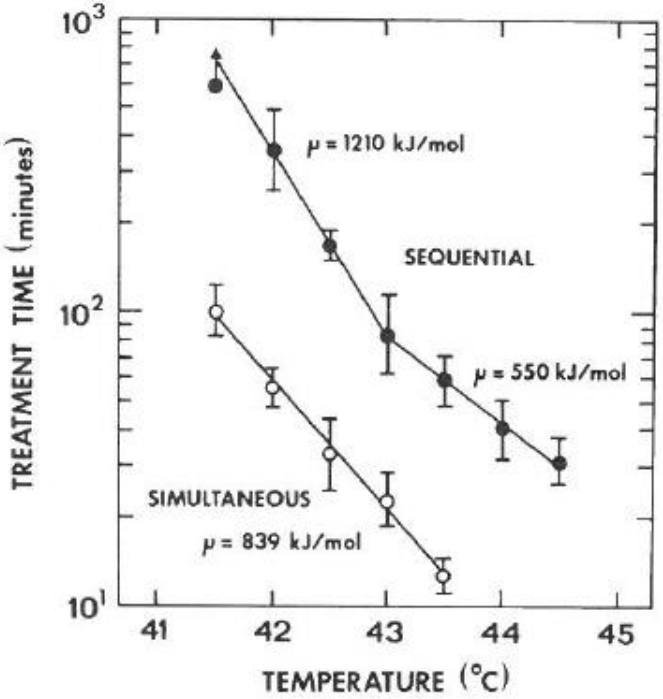




Elming et al. (2019) Cancers







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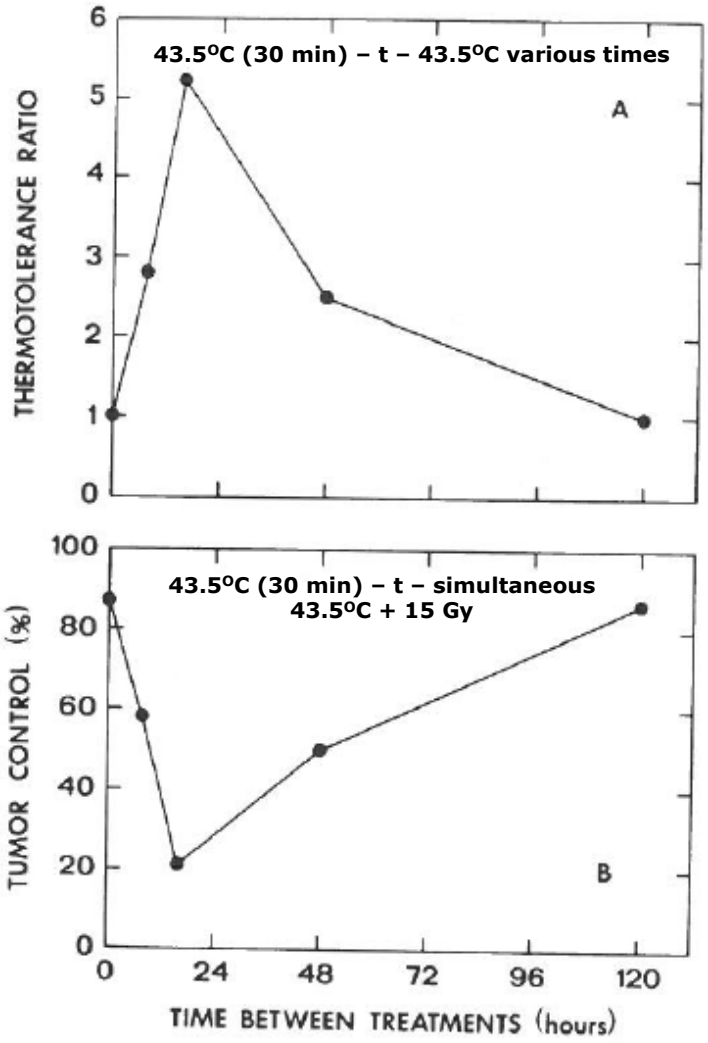
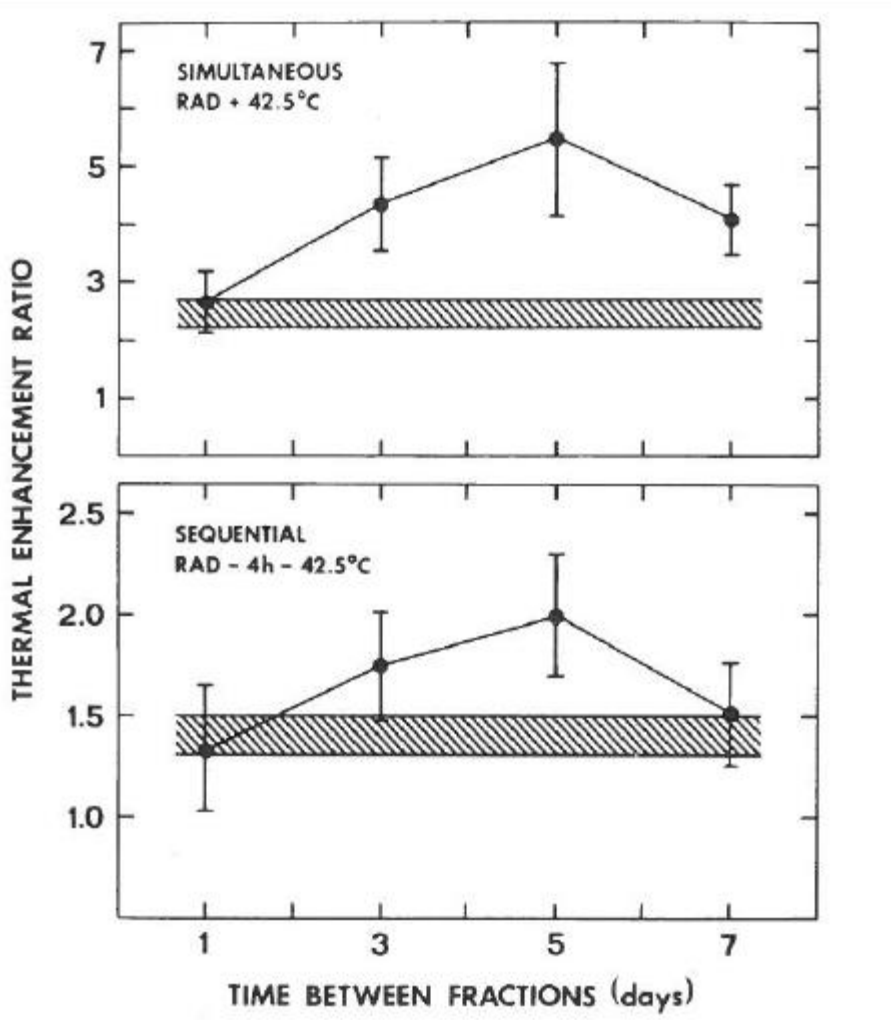
Effect of Thermotolerance on radiation response





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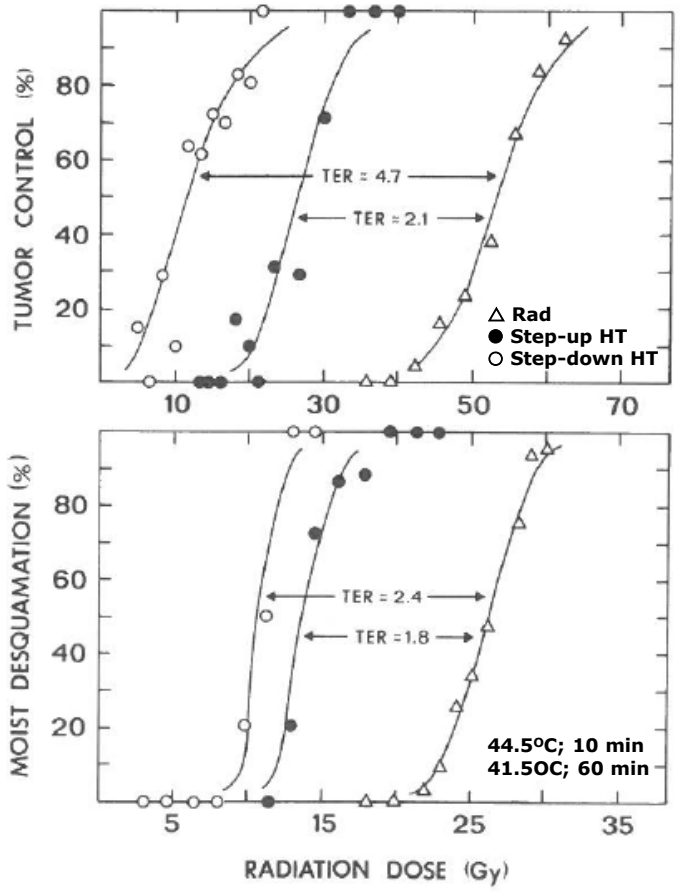
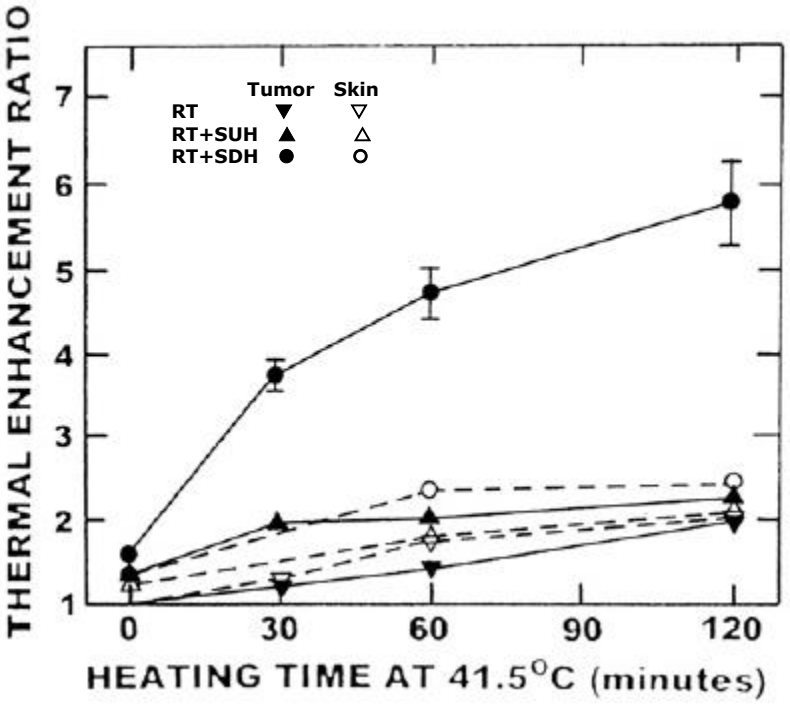
Effect of Step-down (44.5°C-0h-41.5°C) or Step-up heating (41.5°C-0h-44.5°C) on radiation response





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