Hyperthermia in Oncology:
The Hot Topic

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Disclosure Statement

- Owner Integrated Health Clinic, which offers Hyperthermia Treatment

- Co-Investigator of pending Phase II trial “Neoadjuvant local regional hyperthermia for advanced local pancreatic cancer: a randomized clinical trial”

“Those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by fire [hyperthermia]. Those who cannot be cured by fire, they are indeed incurable.”

—Hippocrates (479–377 B.C.)

Hyperthermia through the Ages

- Pitta
- Yang
- Fire
- Heat

- Every traditional medical culture has described hyperthermia, and its uses in healing.
- Ancient texts from India, China, Egypt, Turkey, Middle East and others, contain pictures of various techniques being used to impart heat - in attempts to treat rounded lesions above and below the skin.

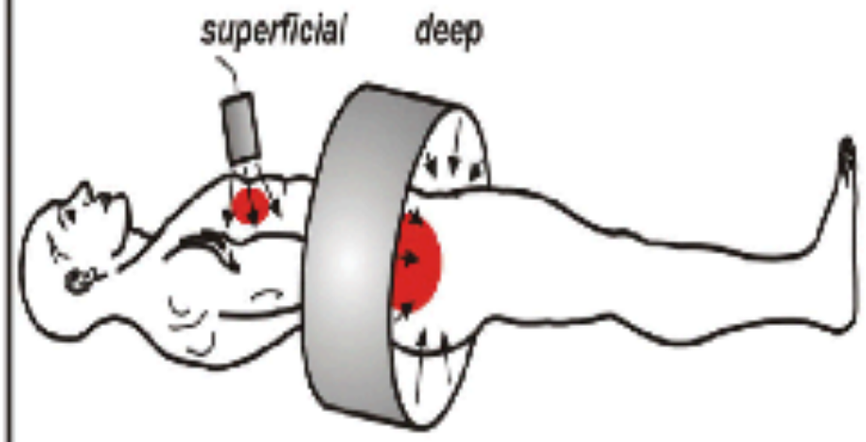
Hyperthermia (HT) Basics

- Causes direct cytotoxicity [1–6]
- Known chemotherapy (CT)sensitizer[7–16]
- Known radiation (RT) sensitizer[17–23]
- Improves tumour oxygenation[24–26]
- Induces P53[27,28]
- Improves delivery of liposomal drugs[29–31]

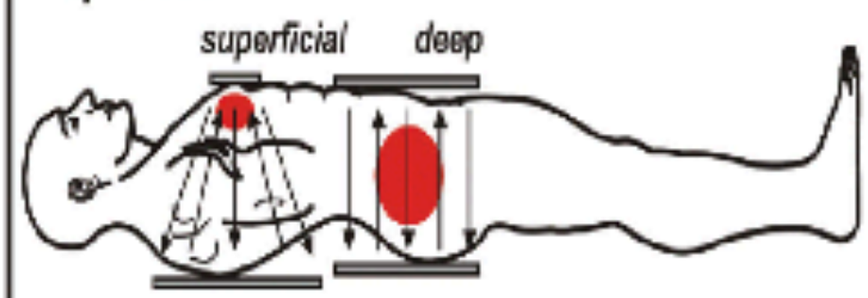
HYPERTHERMIA TECHNIQUES

LOCAL EXTERNAL

- *radiative*



- *capacitive*

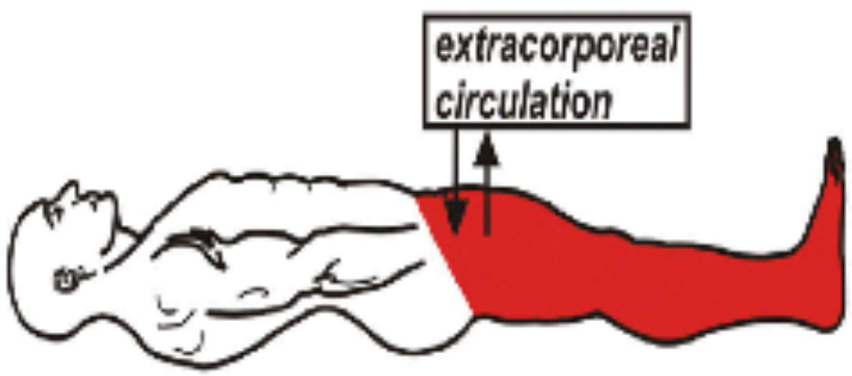


LOCAL INVASIVE

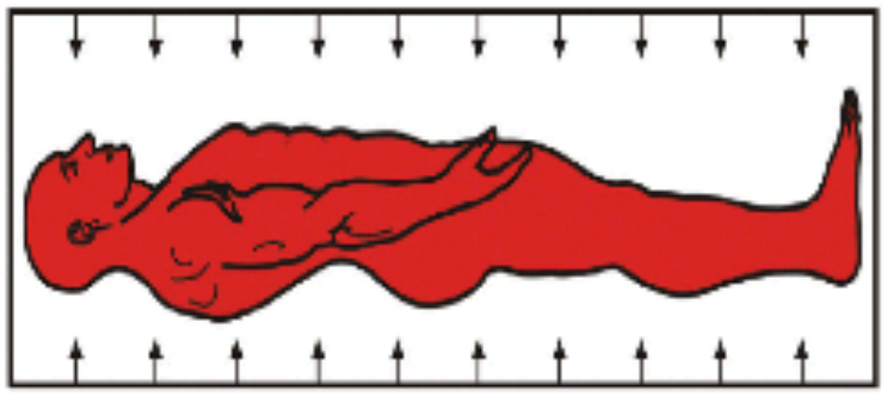
Intraluminal

Interstitial

PERFUSION



WHOLE BODY



Challenges in HT

- The 3 major challenges are;
  - Heating tumours to high temperatures in a precise and reproducible manner*
  - Defining and calculating the required “thermal dose” for efficacy*
  - Measuring temperature (dosimetry);
    - Historically invasive
    - Improved recently with 3D MRI-based thermometry
    - Beyond the scope of today’s lecture
- There has been significant progress on all these issues, particularly in the past decade

HT Findings to Date

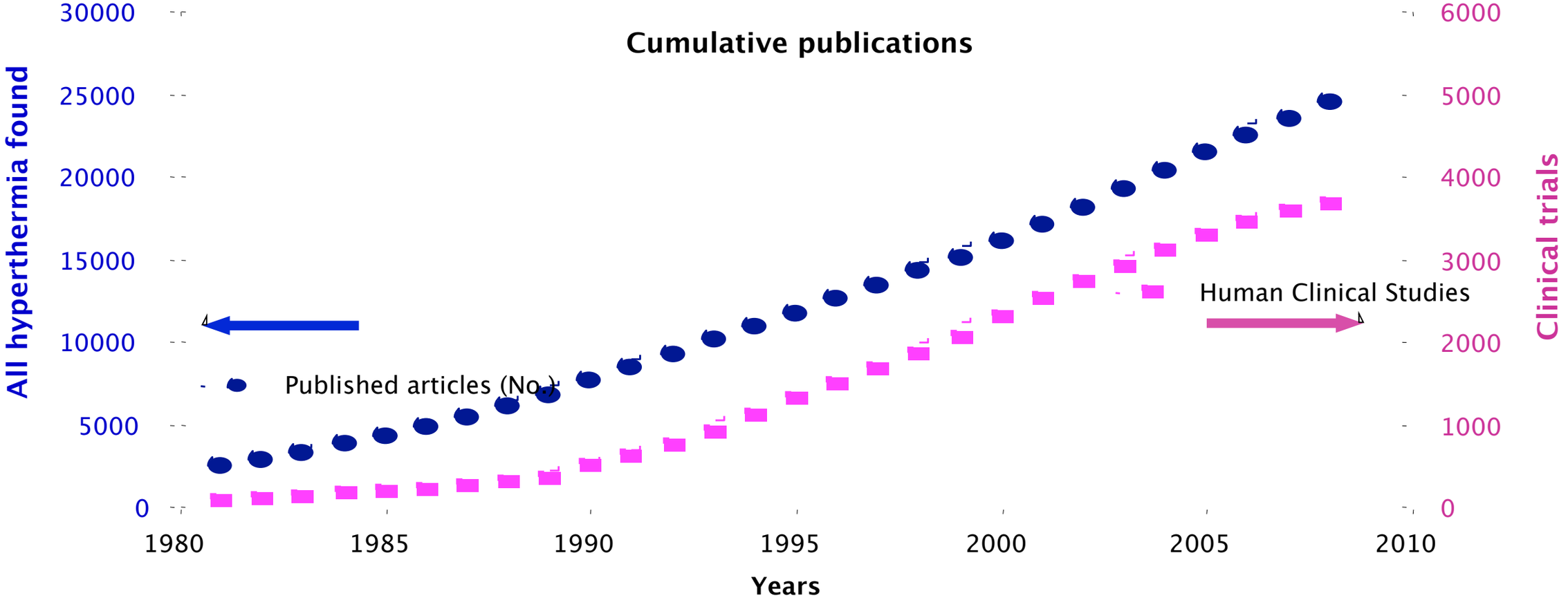
- Many positive published randomized trials on HT in human cancer patients[7–23]

- Most trials on HT + RT and/or CT have demonstrated a significant improvement to;
  - Local tumour control
  - Survival advantage

- Will review most recent & best evidence later in this discussion

Publications on Hyperthermia & Oncology

Hyperthermia became part of the professional handbooks



SEARCH Profile (PubMed, http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed):
(hyperthermia OR heat-treatment OR heat-therapy) AND (oncolog* OR tumor OR cancer OR neoplasm) NOT (malignant-hyperthermia)

Limits of this lecture

- In this lecture HT will be defined as;

  - **40℃ to 45℃ Range:**
    - Average body temperature is 37℃+/- 1.5℃
    - Range desired in local/regional HT
    - Difficult range to accomplish in whole body hyperthermia (WBH)

- Known benefits both below & above this range;
  - Below: Circulatory, Detoxifying & Immunogenic effects (WBH)
  - Above: Ablative indications (Local/Surgical HT)

Mild to Moderate HT: Quick Review

- **Mild HT:**
  - 37℃ to 38.5℃ range
  - Potential benefits include improved circulation and detoxification
  - Most accessible forms of mild HT include;
    - Sauna
    - Hot baths
    - Balneotherapy

- **Moderate Hyperthermia (fever range):**
  - 38.5℃ to 40℃ range
  - Added immunogenic benefits like those seen in infection
  - Most often used range in WBH
    - Requires specialized equipment & screening ECG/exams
    - Requires monitoring rectal temperature, vitals, I.V. fluids

HT Dosimetry:
Arrhenius Relationship

- In HT, this is the math defining “Thermal Dose”, or how much heat is required

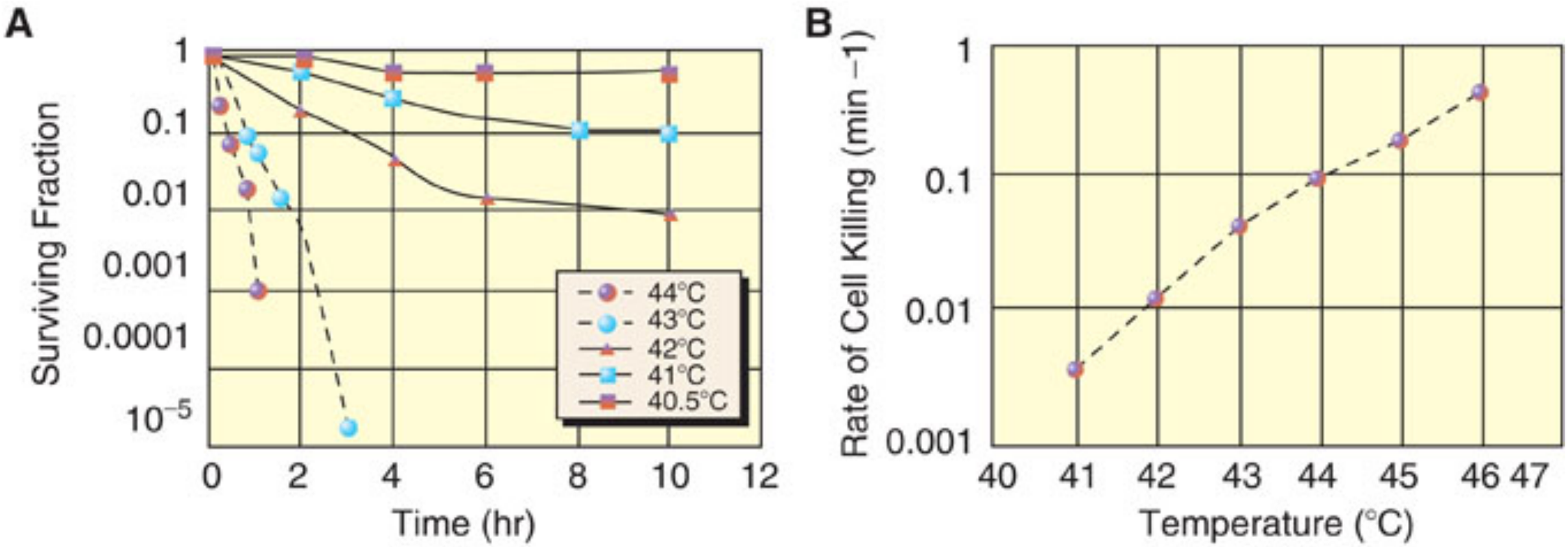
- Defined as the log of the slope (1/ Do) of cell survival curves, as a function of temperature[33] (Fig.1)

- Defines temperature vs. cell killing rate relationship

- Used as measure of thermal dose in human trials[32]

- Arrhenius plots from in vitro and in vivo studies correlate well[35]

Figure 42-1 ■ (A) Cell survival curves for V79 cells, plotted as log of surviving fraction as a function of time of heating at a defined temperature. Source: Data re-plotted from Reference 122. (B) Arrhenius plot from same data. Note change in slope of Arrhenius plot above and below 43℃.



Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.1, 2010

Dosimetry: BreakPoint

- The “breakpoint” is the temperature where the slope changes significantly[32-35]

- The breakpoint for human cells is near 42-43℃
  - Above the breakpoint;
    - Increase of 1.0℃ doubles the rate of cell killing
  - Below the breakpoint;
    - Decrease of 1.0℃ drops rate of cell killing by a factor of 2-4 times

- The change in slope below the breakpoint is largely due to development of thermotolerance during HT

Factors affecting the Arrhenius Relationship

- Three cellular/tissue responses to HT which are known to affect its cytotoxicity include;
  - Thermotolerance
  - Acute Acidification
  - Step-Down Heating
- All 3 factors affect the position and slope of the Arrhenius plot
- Thereby impacting the cytotoxicity of HT significantly (Fig.2)

Thermotolerance

- Refers to the development of resistance to HT from prior exposures to heat[1]

- Repeated heating at temperatures below the breakpoint (<42℃) allows thermotolerance to develop

- Heated cells produce HSP's, particularly HSP70 and HSP27, in response to environmental stressors such as extreme heat, which protect the heated cells against further heating

- Quercetin[36] and other COX-2 inhibitors[37] have been found to minimize thermotolerance, thereby improving HT sensitivity

Acute Acidification

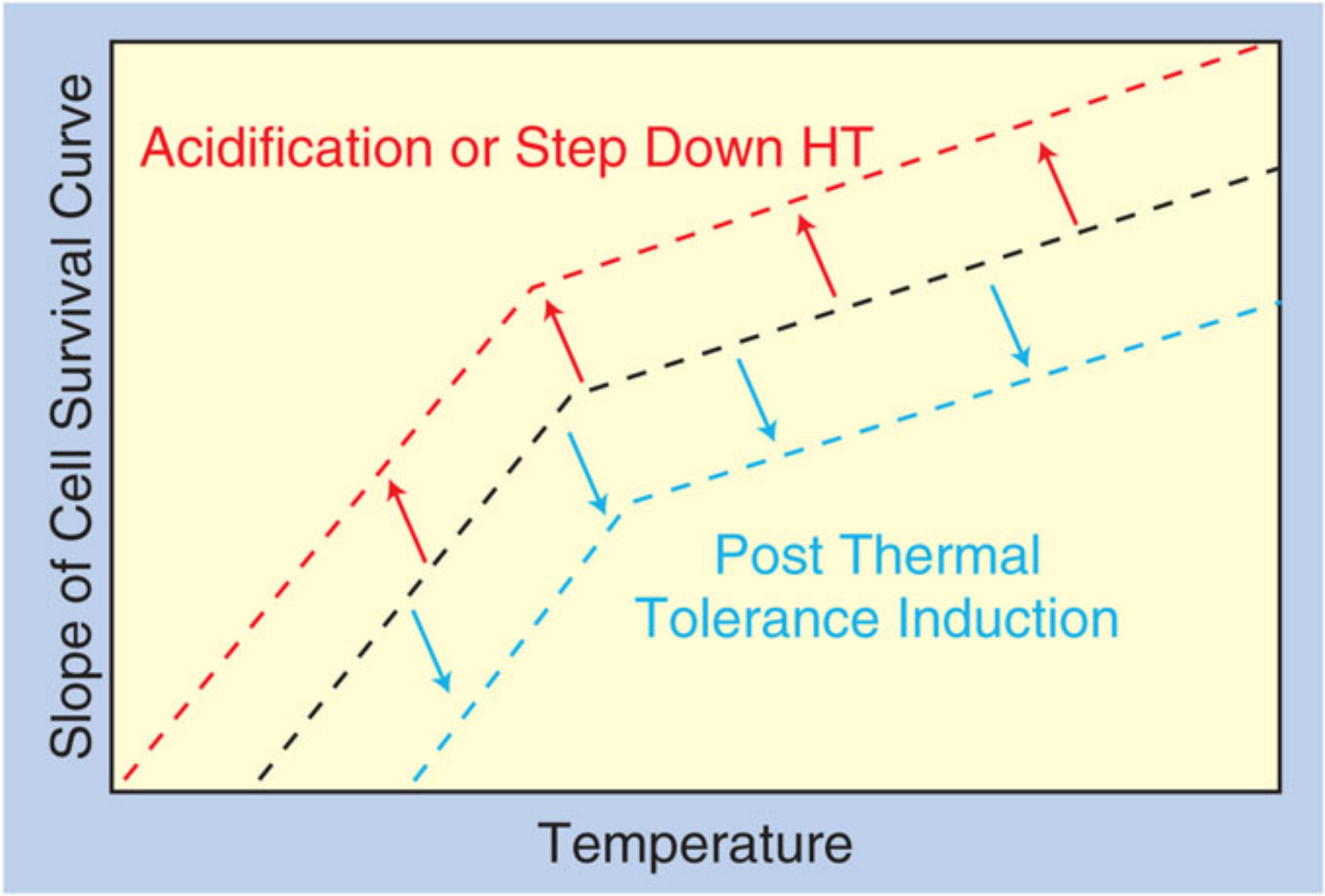
- Increasing acidity in the target tissue sensitizes cells to killing
- Acute acidification shifts Arrhenius plot to the left (Fig.2), causing breakpoint to nearly disappear
- Acute acidification also inhibits thermotolerance
- Methods for acute acidification of the tumour environment have been studied extensively in pre-clinical models and in humans[38-40]
- Administering glucose during HT seems to be the most effective means to acutely acidify[40]

Step-Down Heating

- Involves raising temperatures above the breakpoint, then dropping it below breakpoint for remainder of the treatment[41]

- Occurs clinically when heat is turned down in response to;
  - Pain
  - Excessively high tissue temperatures
  - Perfusion or edema occurs or increases

- Prevents thermotolerance during HT treatment (which shifts Arrhenius plot to the right)



Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.2, 2010

Oxygenation from HT

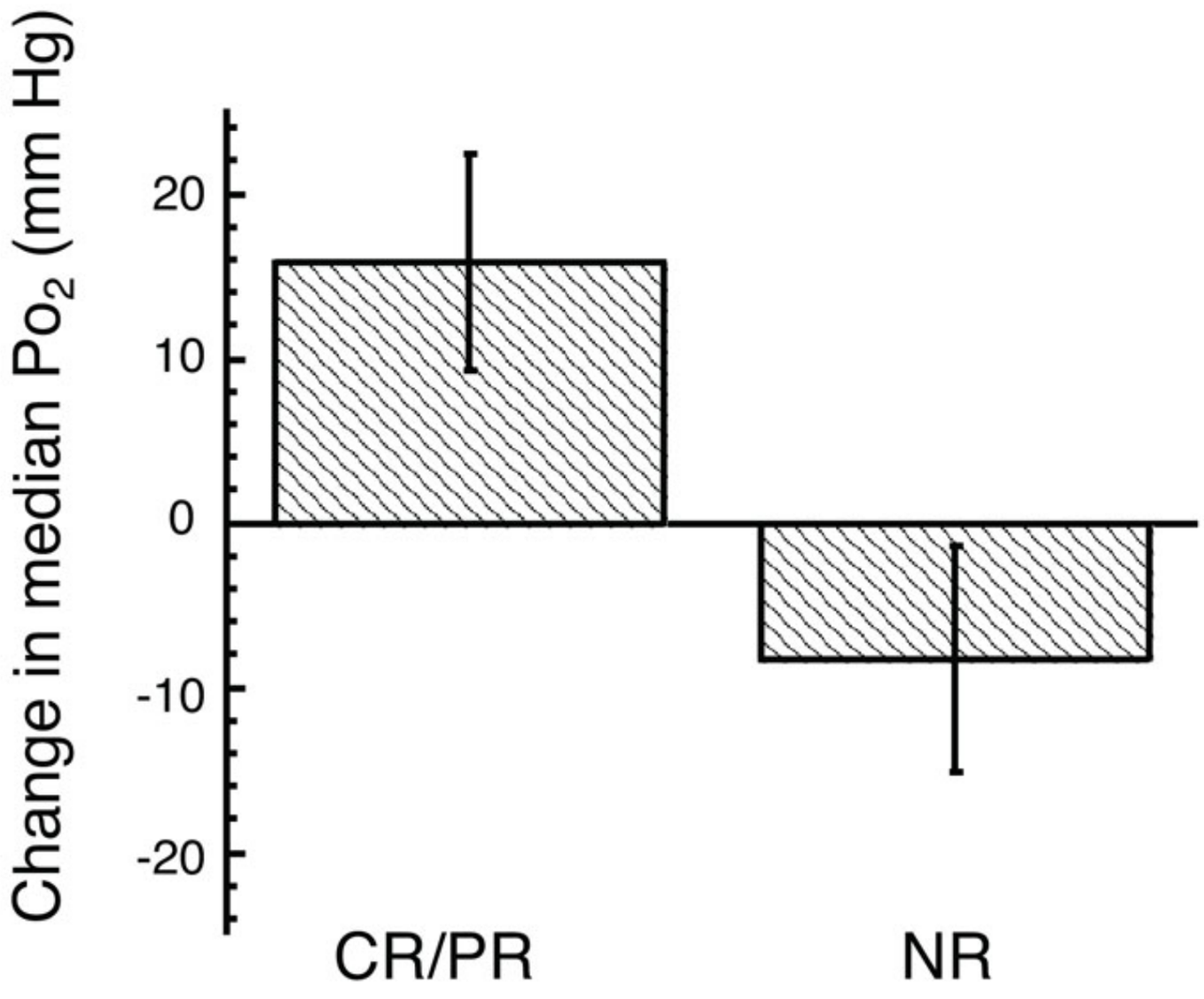
- Some of the clinical benefits of HT result from improvements in oxygenation[42-44]

- Studies in rodent, canine and human tumours have shown improved tumour oxygenation by HT, including breast cancer[42-44]

- Increased oxygenation begins at lower temperatures (40-43℃)

- Some human trials have shown that failure to re-oxygenate after the first HT fraction, significantly reduced the pathologic complete response rate at the time of surgery, breast cancer in this case (Fig.5)[42]

Figure 42-5 ■ Relationship between change in Eppendorf electrode hypoxic fraction, as measured 24 hours post first HT, and clinical response in patients with locally advanced breast cancer. These patients were treated with a combination of Taxol, RT, and HT. Re- oxygenation is clearly associated with those patients who achieved either a complete or a partial response. (Ref 42)



Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.5, 2010

Immune Effects of HT

- Immune enhancing effects of HT include:

  – Enhanced cytotoxic activity of macrophages, T cells & NK Cells[45-47]

  – Enhances maturation and function of dendritic cells [48-50]

  – Improved immune cell-mediated recognition and attack of heated tissue [51-56]

Immune Effects of HT

- Continued Immune Effects....

- HSP's expressed on the surface of heated tumour cells activate NK cell proliferation and thus tumour cell cytotoxicity [27,28,51,53,54]

- HSP/NK cell mechanism makes heated tumour cells more immunogenic [51-54]

- Leads to a cytokine release and increased expression of antigen-presenting cell surface molecules, thus a more effective adaptive immunity [55,56]

Vascular Response to HT

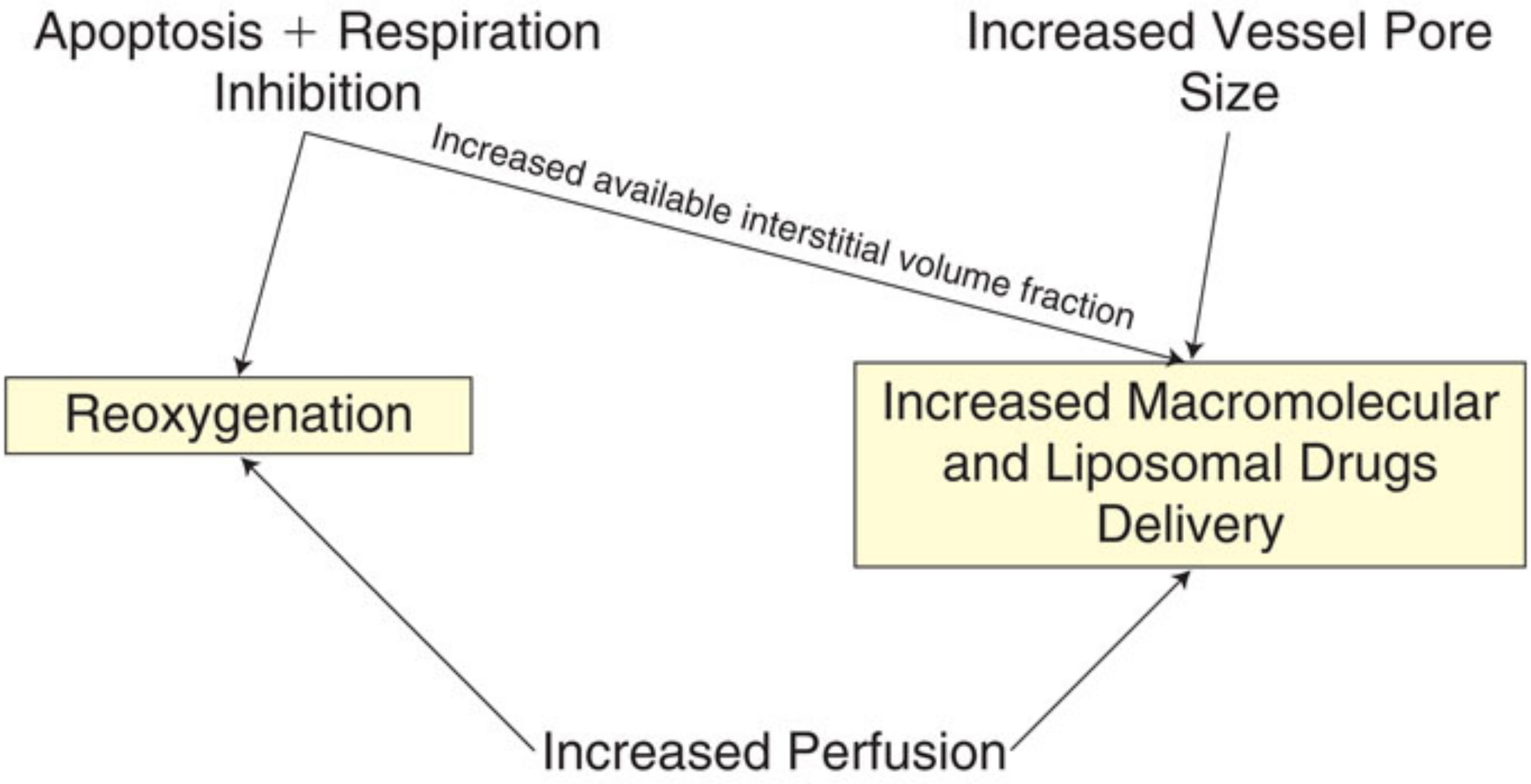
- Increased blood flow is the first tissue reaction to occur at 41℃ to 41.5℃ (in the skin)[57]

- Estimated that muscle/skin perfusion increases approximately 10-fold, whereas tumour perfusion increases by only 1.5 to 2-fold[58]

- At higher thermal doses (>45℃) there is an increased vascular permeability, which can lead to edema and/or vascular stasis/ hemorrhage

- Physiologic changes in tumours at 40-42℃ in Fig.3

Physiological Benefits of Low Temperature Hyperthermia (40-42°C)



Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.3, 2010

Molecular Effects of HT^2

Cell Membrane/Cytoskeleton

- Changes in fluidity and stability of cell membrane
- Changes in Cell Shape
- Impaired Transmembranal Transport
- Changes in Membrane Potential
- Modulation of Transmembranal Efflux Pumps
- Apoptosis Induction

Other Alterations of Cell Function

- Intracellular metabolism of other substrates
- Gene expression, signal transduction

Molecular Effects of HT^2

Intracellular Proteins

- Impairment of Protein Synthesis
- Protein Denaturation
- Aggregation of Proteins at the nuclear matrix
- Induction of HSP-synthesis

Nucleic Acids

- Impairment of RNA/DNA Synthesis
- Inhibition of Repair enzymes
- Altered DNA conformation

Chemosensitizing Effects of HT

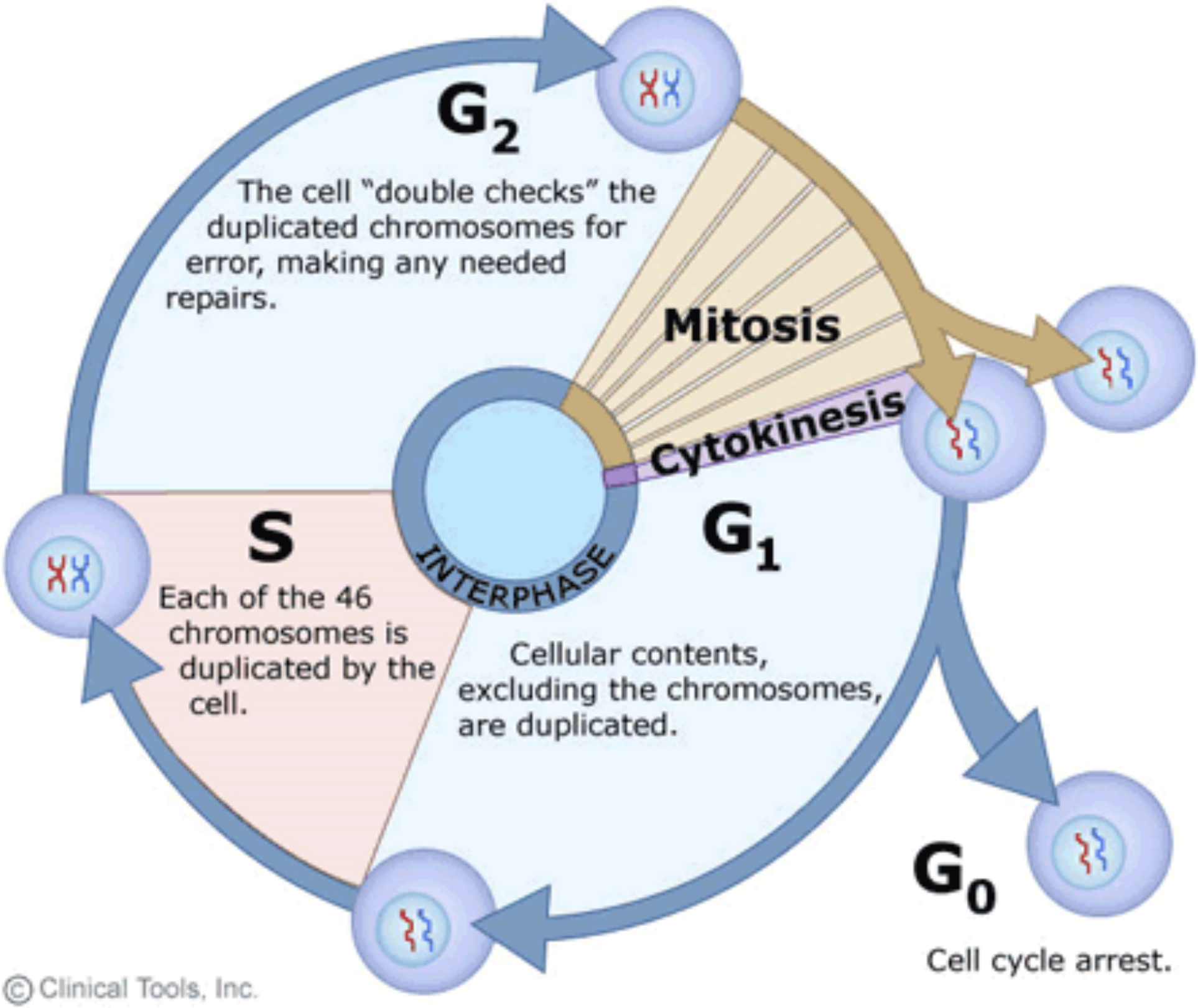
- HT accelerates the primary mode of action of various CT drugs including[7-16];
  - Alkylating action
  - Induced protein damage & DNA strand breaks
  - Production of oxygen radicals

- Many CT agents shown to improve with HT, including; melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosureas, bleomycin and mitomycinC[59-61]

- Lack of Interaction has been found with etoposide and vinca alkaloids[59]

Complimentary Effects of **Chemotherapy & Hyperthermia**

Effects/Method	Chemotherapy	Hyperthermia
Place of Primary Activity	Near Arteries	Far from arteries
Reaction Rate	Normal	Enhanced
Chemo Penetration	Low, due to high pressure	Enhanced via electro-osmosis
Chemo Metabolism	Normal	Enhanced
Chemo Selection	Limited by chemical reaction	Local enhancement
Cell Division	Acts in M + G2 Phase	Acts in S Phase
Activity	No Activity in G0 Phase	Decreases time spent in G0 Phase
Treatment Failure	Blood/Organ failure and tolerance	Resensitizes to chemo & decreases liver and kidney stress


G2
The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
Mitosis
Cytokinesis
G1
INTERPHASE
S
Each of the 46 chromosomes is duplicated by the cell.
Cellular contents, excluding the chromosomes, are duplicated.
G0
Cell cycle arrest.
© Clinical Tools, Inc.

Radiosensitizing Effects of HT

- Complementary effects between RT and HT include[17-23,62,63];
  - Cells in S-phase relatively resistant to RT, but most sensitive to HT
  - Hypoxic cells 3 times more resistant to RT than aerobic cells, whereas no difference in thermal sensitivity between aerobic and hypoxic cells
  - Good evidence in human soft tissue sarcoma and locally advanced breast cancer, that HT causes re-oxygenation, further improving RT response[18,22]
  - HT inhibits the repair of protein damage, by inactivating crucial DNA repair pathways[62,63]

Complimentary Effects of **Radiotherapy & Hyperthermia**

Effect/Method	Ionizing Radiation	Hyperthermia
Cell Cycle Specificity	Acts in M + G1 Phase	Acts in S Phase
pH-Dependance	Acts in relatively ALKALINE environments	Acts in relatively ACIDIC environments
Oxygen Specificity	Acts in Well-Oxygenated environments	Acts in Hypoxic tissue

Phase 3 Trial:
HT in Sarcoma

- Recent phase III, randomized, multi-centre (EU & US), clinical trial comparing HT+EIA (etoposide, ifosfamide and adriamycin) vs EIA alone[7]

- 341 patients with locally advanced soft tissue sarcomas with a median follow-up of 34 months

- 2 year disease free survival (DFS) 70% (HT/EIA) vs 57% (EIA)

- 2 year local progression free survival (LPFS) 92% (HT/EIA) vs 80% (EIA)

- Patients more likely to experience local progression or death in EIA-alone group (relative hazard [RH] 0·58, 95% CI 0·41–0·83; p=0·003)

Phase 3 Trial:
HT in Sarcoma

- Treatment response rate was 28.8% (EIA/HT) vs 12.7% EIA (p=0·002)

- Overall survival (OS) was better in the EIA/HT group (p=0·038)

- As a result of this study - The National Clinical Practice Guidelines in Oncology for Soft Tissue Sarcoma (NCCN), now recommends HT + CT for Stage II, III and IV soft tissue sarcomas of the trunk and the extremities

- Used to be recommendation in only Stage IV, but the results of this study showed a significant benefit for Stages II, III and IV

Phase 3 Trial:
HT in Cervical Carcinoma

- 361 patients with previously untreated locally advanced pelvic tumours randomized to RT vs RT+HT[17]

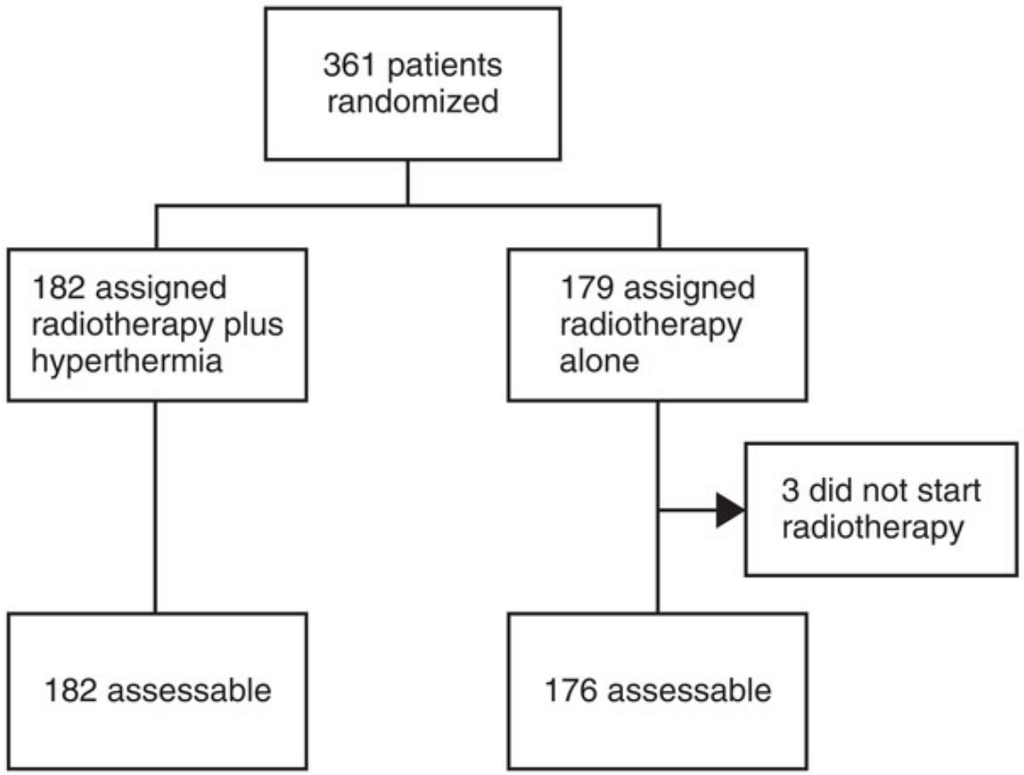
- Included patients with rectal, bladder, and cervical carcinoma

- Complete response (CR) rates were 39% after RT alone and 55% after RT+HT ($p \leq 0.001$)

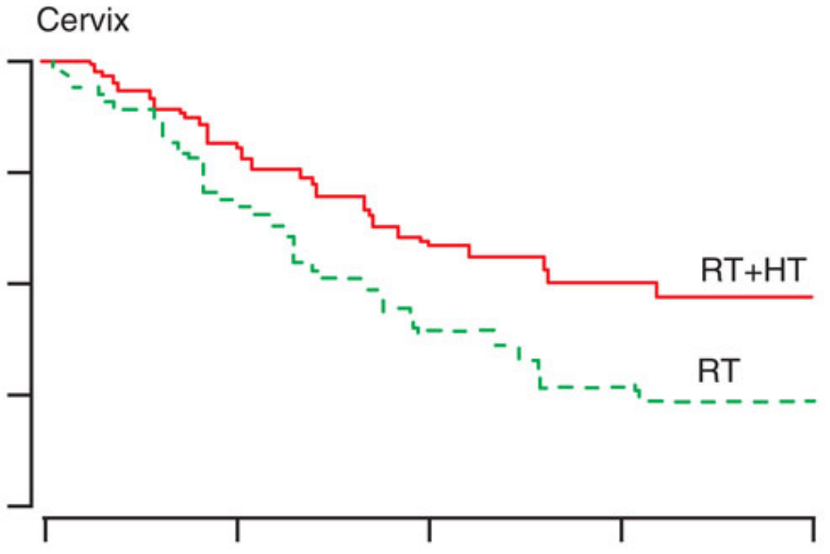
- Results best in cervical carcinoma where CR rate following RT + HT was 83% compared with 57% after RT alone

- 3-year survival was 27% RT alone vs. 51% RT+HT ($p = 0.003$)

A



B



Number at risk

RT+HT	58	43	26	17	13
RT	56	36	17	9	6

Viglianti BL, Stauffer P, et al. Cancer Medicine 8, Chapter 42, Fig.8, 2010

Phase 3 Trial:
HT in Breast Cancer

- 5 independent phase 3 trials were combined for this international collaborative study[19]

- Patients randomized to RT or RT+HT

- Significant improvement in CR for HT + RT vs. RT alone, 59% and 41% respectively (odds ratio 2.3 (95% CI 1.4-3.8))

- Greatest effect observed in patients with recurrent lesions in previously irradiated areas, since further irradiation was limited to low dosages

- Did not show an overall survival advantage

Phase 3 Trial:
HT in Head & Neck Cancer

- This study randomized 65 patients to RT alone versus RT + HT[23]

- HT twice weekly, 72 hours apart

- Stage III: CR 58% RT+HT vs 20% RT alone

- Stage IV: CR 38% RT+HT vs 7% RT alone

- No additional benefit in stage I & II, with> 90% achieving a CR in both groups

Phase 3 Trial:
HT in Malignant Melanoma

- 70 patients with metastatic or recurrent malignant melanoma lesion(s) were randomized to RT or RT+HT[21]

- Significant benefit for RT+HT with a 2-year local control of 46% vs. 28% RT alone

- Quality assurance was an issue in this trial since only 14% of treatments achieved 43℃ for 60 minutes, the target thermal dose for treatment

- Despite this inconsistency in thermal dose, positive benefits were seen - presumably due to the known benefits at lower doses (40-42℃ (Fig. 3))

Phase 3 Trial:
HT in Glioblastoma Multiforme

- University of California San Francisco study comparing interstitial HT +Brachytherapy vs. Brachytherapy alone[11]

- 112 patients with glioblastoma multiforme were accrued, 79 qualified for brachytherapy and were randomized

- Remaining patients were dropped from the protocol due to disease progression

- Both time to tumour progression and overall survival were significantly improved vs. brachytherapy alone

- Two-year survivals were 31% and 15%, respectively

HT Availability in USA

- hyperthermia-and-cancer.com/2012/01/hyperthermia-cancer-treatment-centers-in-the-usa/
- hyperthermia.mc.duke.edu/
- bichercancerinstitute.com/
- radonc.ucsf.edu/treatment_programs/hyperthermia.html
- cancercenter.com/conventional-cancer-treatment/radiation-therapy/local-hyperthermia.cfm

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Hyperthermia in Oncology:
The Hot Topic

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