Hyperthermia

Chapter 28

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Radiobiology for the Radiologist

Introduction

- Heat was used in many cultures for almost any disease including cancer
  - First case of a patient with a breast tumor treated with hyperthermia was described more than 3,500 years ago
  - In 1866 a case was described where sarcoma disappeared after prolonged infection with a high fever causing bacteria
  - 1898 marked regression of carcinomas of the uterine cervix after local hyperthermia

Recent history

- Studies in the 1970s – 1980s demonstrated highly quantifiable, time dependent cytotoxic effects of heat (41-45ºC) on cells
  - Similar to highly reproducible and predictable effects of radiation
- In combination with radiation heat was found to have both additive and synergistic radiosensitizing properties

Hyperthermia definition

- *Hyperthermia* is defined as a therapeutic procedure used to raise the body or local tissue temperature to about 41-43°C (42.5°C threshold)
- It is almost always used as adjuvant therapy as it provides a possibility for synergy with different actions of conventional therapies
  - Combination with radiotherapy and/or chemotherapy results in higher response rates, improved tumor control, better palliative effects and/or better overall survival rates in some tumor types

Direct effects of hyperthermia

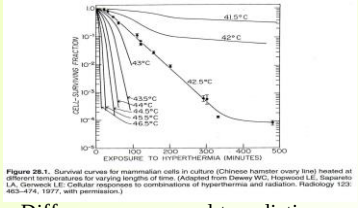


Figure 28.1. Survival curves for mammalian cells in culture (Chinese hamster ovary line) heated at different temperatures for varying lengths of time. (Adapted from Dewey WC, Hopwood LE, Sapareto LA, Gerweck LE: Cellular responses to combinations of hyperthermia and radiation. Radiology 123: 463–474, 1977, with permission.)

The general shape of cell survival curves is similar to those obtained for x-rays

- Differences compared to radiation:
  - Two parameters: temperature and exposure time
  - Low temperature curves flatten out (thermal tolerance)
  - The amount of energy involved in cell inactivation is ~1000 times higher in hyperthermia

Direct effects of hyperthermia

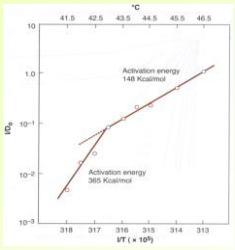


Figure 28.2 An Arrhenius plot for heat inactivation of mammalian cells in culture. The reciprocals of the D_0 values obtained for Figure 28.1 are plotted versus 1/T

- The change in slope identifies a "breakpoint" of ~43ºC for human cells
- The difference in activation energy corresponds to a difference in cell killing rate
- Different mechanisms or development of thermal tolerance may be involved

Cytotoxic effect of hyperthermia

- The activation energy for heat cytotoxicity is similar to that for protein denaturation (130-170 kcal/mol)
- The target for heat cell killing in this temperature range resides in cellular proteins
- Additional evidence is the importance of heat shock proteins (HSPs) in protecting thermotolerant cells from thermal damage
  - One of the primary functions of HSPs is to stabilize and refold other proteins that have been denatured or damaged
  - HSPs production is enhanced in response to such events

Biological effects of hyperthermia vs. radiation - additive

- Since killing is associated with degradation or denaturation of proteins, hyperthermia induces effects in both the nucleus and cytoplasm
  - Radiation cell killing primarily damages DNA
- In organized tissues heat damage occurs more rapidly than radiation damage
  - Both differentiated and dividing cells are killed by heat
- The DNA repair process is heat-sensitive, making cells in S-phase a primary target
  - Cells in M and G2 phases are the most radiosensitive

Role of tumor micro-environment

- Malignant and normal cells demonstrate no difference in their response to heat under identical culture conditions
- The combination of low pH, low oxygen tension, and lack of glucose and other nutrients tends to make cells extremely responsive to elevated temperatures
- The microenvironment of cells in solid tumors is particularly conducive to heat sensitivity

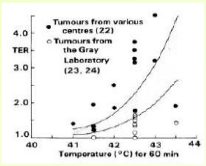
Biological effects of hyperthermia vs. radiation - sensitizing

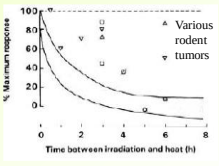
- At the cellular level: the events associated with heat radiosensitization involve DNA damage and the inhibition of its repair
  - The role of heat is to block the repair of radiation-induced lesions
- At the tissue level: even mild hyperthermia promotes changes in tumor environment, providing sensitization via oxygenation, change in pH, metabolism, protein/gene expression, and vascular perfusion

Thermal enhancement ratio

- The thermal enhancement ratio (TER) is defined as the ratio of doses of x-rays required to produce a given level of biologic damage with and without the application of heat
- Characterizes the extent of the interaction of heat and radiation (both additive and sensitizing effects)
- The TER has been measured for various normal tissues (skin, cartilage, and intestinal epithelium)
- The data form a consistent pattern of increasing TER with increasing temperature

Thermal enhancement ratio





- TER for tumors (points) and normal tissues (range indicated by two curves)
- TER also depends on temperature, time at that temperate, and time interval between irradiation and heat
- In clinical evaluations TERs of only 1.15 to 1.5 were observed

Therapeutic gain factor

- The therapeutic gain factor can be defined as the ratio of the TER in the tumor to the TER in normal tissues
- For the same environmental conditions normal tissues and tumor have the same sensitivity to heat
- The therapeutic gain is typically achieved due to higher temperature and more heat-sensitive microinviroment of the tumor

Thermal tolerance

- Resistance to subsequent heating was found in cell cultures, mediated by heat-shock proteins (HSP)
  - HSP are "chaperon" molecules, assisting with folding and unfolding of macromolecular structures; they are also produced after treatment with other toxic agents, e.g., arsenic and ethanol
- Possible problem scheduling fractionated heat treatments
- Recent findings: heat-induced radiosensitization is not subject to thermal tolerance
- The effect of reduced direct cell killing is overcompensated *in situ* by radiosensitization
- Current effort in exploration of HPS role in promoting antitumor immune response

Immunologic effects of hyperthermia

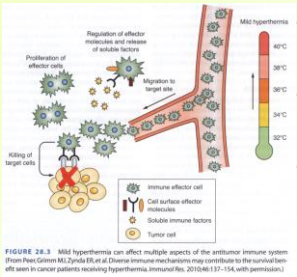


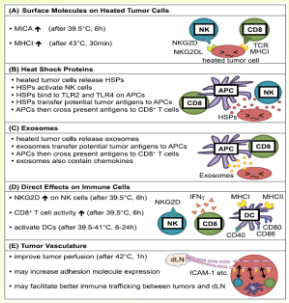
FIGURE 28.3 Mild hyperthermia can affect multiple aspects of the antitumor immune system (From Peer,Grimm MJ,Zynda ER,et al.Diverse immune mechanisms may contribute to the survival benefit seen in cancer patients receiving hyperthermia. Immunol Res. 2010;46:137–154,with permission.)

- When body temperature is elevated through fever, it is usually <40°C
- Reports of improved survival in patients with highest fevers
- Enhancement in immune system response (including adaptive response through effector T-lymphocytes) is implicated

Immunologic effects of hyperthermia

- *Innate* immunity refers to the cells and the proteins that are present in the body and are ready to fight diseases at all times; the cells of *adaptive* immunity are only called to action if pathogens overcome the power of innate immunity
- Immune system players:
  - Cytokines - a large group of proteins that are secreted by specific cells of immune system; they are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis.
  - NK – natural killer cell, part of the innate system, stimulated by HSPs
  - CD8+ T cells – adaptive system
  - APC – antigen-presenting cell, example: DC - dendrite cell (act as messenger between innate and adaptive systems)

Immunologic effects of hyperthermia



S. Toraya-Brown, S. Fiering, Local Hyperthermia as Cancer Immunotherapy, Int J Hyperthermia, 2014; 30(8): 531–539

Mechanisms of immune activation:
(A) Heated tumor cells increase the surface expression of signaling molecules, making the tumor cells more sensitive to lysis by NK cells and CD8+ T cells, respectively
(B) Heated tumor cells release HSPs, which activate NK cells and APCs. HSPs contain potential tumor antigens, and APCs take up the HSP antigen complex and cross present the antigen to CD8+ T cells.
(C) Heated tumor cells release exosomes. Exosomes also contain potential tumor antigens, and APCs take up the antigen and cross present the antigen to CD8+ T cells.
(D) Immune cells, such as NK cells, CD8+ T cells and DCs, in the tumor also get heated and become activated.
(E) The tumor vasculature becomes more permeable and may have increased adhesion molecule expression after heating, which may facilitate better trafficking of immune cells between the tumor and dLN

Immunologic effects of hyperthermia

Heating tumors can elicit anti-tumor immune responses by

(1) tumor cells stimulation of the immune system through expression of surface signaling molecules and release of HSPs and/or exosomes

(2) directly activating intra-tumoral immune cells such as NK cells, CD8+ T cells, and DCs, and

(3) improving immune-cell trafficking between the tumor and lymphoid organs (tumor-specific resistance against re-challenge was also observed – possibly a temperature range for immune stimulation)

Immunologic effects of hyperthermia

- Current evidence includes:

  (1) enhanced immogenicity and HSP expression seen after tumor cells are heated

  (2) thermally enhanced immune effector cell activation and function, and

  (3) thermally enhanced vascular perfusion and delivery or trafficking of immune effector cells to tumors

Thermal dose

- The heat-induced cytotoxicity of tumor cells is dependent on both temperature and time
- Assessment of thermal dose involves time-integrated temperature analysis
- Obtaining this information in patient-specific treatments is hindered by physiologic factors, temperature non-uniformity, etc.
- Approach suggested by Sapareto and Dewey: use information from the Arrhenius plot and a concept of "cumulative equivalent minutes at 43ºC" (CEM 43ºC)

Thermal dose

- Above T= 43ºC - effects of a 1°C rise of temperature is equivalent to a reduction of time by a factor of 2:

$$\frac{t_2}{t_1} = 2^{T_1 - T_2}$$

- Below - an increase in temperature by 1°C requires that time be decreased by a factor of 4 to 6:

$$\frac{t_1}{t_2} = (4 \text{ to } 6)^{T_1 - T_2}$$

Thermal dose

- The heat dose associated with a changing temperature is calculated as the sum of equivalent heating times at 43°C for each temperature

$$CEM\,43^{\circ}C = tR^{(43-T)}$$

- *CEM* 43ºC, "cumulative equivalent minutes at 43ºC", is calculated from the heat exposure time *t*, the given temperature *T*, and a constant *R* which is 0.5 when the T > 43ºC, and 0.25 if it is T < 43ºC
- Parameter *CEM* 43ºC T_{90} - the number of CEM at 43°C exceeded by 90% of the monitored points within the tumor is used to evaluate results of clinical trials

Clinical trials

- Clinical trials are usually completed in phases I through III (phase IV is often used by pharmaceutical companies for drugs to receive FDA approval)
- Phase I – designed to test the initial safety of a drug, device, treatment modality, or a combination
- Phase II – test efficacy, and dose-response
- Phase III – compare the proposed research drug, device, or modality with standard treatment
- Randomized trials - patients are assigned to a particular treatment by some *random* mechanism
- *Prospective* (interventional or observational) studies vs *retrospective*

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- An early Radiation Therapy Oncology Group (RTOG) phase III trial that included patients with various types of superficial tumors yielded well-publicized disappointing results in the late 1980s
  - Showed only a modest benefit of addition of heat
  - Only in patients with tumors that were less than 3 cm
- It was quickly realized that the ability to actually heat tumors and monitor the temperature adequately varied enormously from center to center
- By now at least 10 randomized clinical trials demonstrated clear benefits of hyperthermia as adjuvant treatment

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 1: patients with locally advanced pelvic tumors; done by a Dutch group, which tested the use of radiation alone versus radiation and hyperthermia
- All tumors showed improved response, but most of the benefit appeared in patient with cervical carcinoma:
  - The complete response (CR) rate following RT+HT was 83% compared with 57% after RT alone.
  - Three-year survival was 27% in the RT-alone group of cervix cancer patients, 51 % in the RT+HTgroup (p=0.003)
  - More recent (2008-2009) long-term following continues to demonstrate significant survival benefit in the patients who received hyperthermia
- Recent development: addition of cisplatin to RT+HT

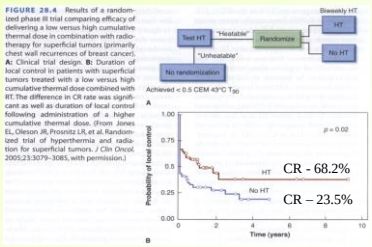
Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 2: Recurrence of breast cancer in chest wall; combined results of 7 separate trials
- Demonstrated significant improvements in patients receiving HT+RT vs. RT-only group
  - CR of 67% in HT+RT group vs. 31% in RT-alone
- The greatest effect was observed in patients with lesions in areas that had previously been irradiated, thus limiting the ability of those patients to receive optimal subsequent irradiation

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 3: Superficial malignancies (mostly recurrence of breast cancer in chest wall); single institution *prospective* trial by Jones et al.
- For the first time tumors were evaluated for "heatability" prior to randomization
- CR of 66% in HT+RT group vs. 42% in RT-alone
- Again, previously irradiated patients had the greatest benefit, showing a 68.2% response rate in the HT+RT group vs. 23.5% in the RT-alone group

Phase III clinical trials: hyperthermia in enhancing radiation therapy



- Example 3: Recurrence of breast cancer in chest wall

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 4: Head and neck cancer; conducted by Valdagni et al.; patients with advanced stages; evaluated both primary site and neck nodes
  - Patients in stage III receiving RT+HT had a 58% CR compared with 20% in the RT group
  - Similarly, patients with stage IV disease achieved a CR of 38% compared with 7% for those receiving RT alone
- In a separate trial by the same group metastatic cervical lymph nodes in patients with advanced local regional squamous cell carcinoma were heated:
  - The CR rate was 83% for RT+HT versus 41 % for radiation alone
  - 5-year survival was 0 for RT alone and 53% in the RT+HT group

Phase III clinical trials: hyperthermia in enhancing radiation therapy

- Example 5: Glioblastoma multiforme; conducted by Sneed et al. at UC SF; evaluated interstitial HT in combination with brachytherapy implants
- Even in this rapidly progressing type of cancer, both times to tumor progression and 2-year survival were significantly improved for patients who received HT compared with those treated with brachytherapy alone (31% vs. 15%)
- However, toxicity appeared to be slightly greater in patients who received hyperthermia

GBM - a fast-growing glioma that develops from star-shaped glial cells; median survival rate of ~15 months; 5-year survival rate of ~4%

Phase III clinical trials: hyperthermia in enhancing radiation therapy

TABLE 21-2 Key Phase III Trials: Hyperthermia Combined with Radiotherapy

Tumor Type/ Location	Type of Trial	N	Rx ARM RT	Rx ARM RT + HT	RT Dose (Gy)	Hyperthermia No. Fx	Hyperthermia Mean Tx Time	Hyperthermia Thermal Dose Goals/ Reported Data	Endpoints Control Arm (RT)	Endpoints Treatment Arm (RT + HT)	Significance ($p < .05$)
***van der Zee*[111]**											
Pelvic	Multicenter	358	176	182	—	—	—	1/wk up to 5 Tx (1-4 h after RT)	Target = 60 min at 42° C Average total HT = 90 min	CR 39% at 3 mo 3-yr OS 24% 3-yr LC 26%	CR 66% at 3 mo 3-yr OS 30% 3-yr LC 36%	Yes Yes Yes
Rectal	—	143	71	72	46-50	—	42 days	—	—	CR 15 % at 3 mo 3-yr OS 22% 3-yr LC 8%	CR 21% at 3 mo 3-yr OS 13% 3-yr LC 16%	No No NR
Bladder	—	101	49	52	66-70	—	48 days	—	—	CR 51% at 3 mo 3-yr OS 22% 3-yr LC 30%	CR 73% at 3 mo 3-yr OS 28% 3-yr LC 42%	Yes No No
Cervical	—	114	56	58	42-	23-28	48 days	—	—	CR 57% at 3 mo 3-yr OS 27% 3-yr LC 41%	CR 83% at 3 mo 3-yr OS 51% 3-yr LC 61%	Yes Yes Yes
***Sneed*[108]**											
Glioblastoma (after RT)	Single institution	68	33	35	59.4 60 Gy	33	32 days 100 hr	2 Fx (before and after RT)	Median CEM43T_{90}: 14.1 Median CEM43T_{90}: 74.6	TTP median 33 wk TTLTP 35 wk 2-yr OS: 15% Median survival 76 wk	TTP median 49 wk TTLTP 57 wk 2-yr OS 31% Median survival 85 wk	Yes Yes Yes

Phase III clinical trials: hyperthermia in enhancing radiation therapy

TABLE 21-2 Key Phase III Trials: Hyperthermia Combined with Radiotherapy—cont'd

Tumor Type/ Location	Type of Trial	N	Rx ARM RT	Rx ARM RT + HT	RT Dose (Gy)	Hyperthermia No. Fx	Hyperthermia Mean Tx Time	Hyperthermia Thermal Dose Goals/ Reported Data	Endpoints Control Arm (RT)	Endpoints Treatment Arm (RT + HT)	Significance ($p < .05$)
***Emami*[95]**											
Various	Multicenter	173	87	86	Prior + study dose <100 Gy	—	1 day	1 or 2 (before RT + after RT)	Goal: Tmin 43° C for 60 min	CR 54% 2-yr LC 37% 2-yr OS 29%	CR 57% 2-yr LC 43% 2-yr OS 36%	No No NR
Head and neck		75	35	40	Prior + study dose <100 Gy			1 or 2 (before RT + after RT)	Goal: Tmin 43° C for 60 min	CR 52% PR 37%	CR 62% PR 10%	No No
Pelvis		75	37	38	Prior + study dose <100 Gy			1 or 2 (before RT + after RT)	Goal: Tmin 43° C for 60 min	CR 57% PR 8%	CR 60% PR 10%	No No
***Vernon*[96]**											
Breast	Multicenter	306	135	171	29-50 Gy ± boost	Varied	2-5 wk	1 to 8	Goal: T ≥42.5° C q 30 min	CR 41% 2-yr OS 40%	CR 59% 2-yr OS 40%	Yes No
***Overgaard*[97]**											
Melanoma	Multicenter	66	65	63	24-27	3	8 days	3	Goal: 43°C q 60 min	CR 35% at 3 mo	CR 62% at 3 mo	Yes
		Patients had more than one tumor			24-27	3	8 days	3	Goal: 43°C q 60 min	5-yr LC 26% RR (RT + HT vs. RT alone): CR = 4.01; 2-yr LC = 1.73%	5-yr LC 46%	Yes
***Sugimachi*[98]**											
Esophagus	Single institution	66	34*	32*	30 Gy	13	3 wk	6	42.5° to 44° C q 30 min	Downstaging effect: 44% CR 8% 3-yr OS 24%	Downstaging effect: 69% CR 26% 3-yr OS 50%	Yes Yes NR

Phase III clinical trials: hyperthermia in enhancing radiation therapy

Tumor Type/ Location	Type of Trial	N	RT	RT + HT	RT Dose (Gy)	No. Fx	Mean Tx Time	Thermal Dose Goals/ Reported Data	Control Arm (RT)	Treatment Arm (RT + HT)	Significance ($p < .05$)
***Vaitkus*[99]**											
Head and neck nodes		41	21/22 nodes	16/18 nodes	64-70 Gy	NR	30 days	3 vs. 6 Fx	Goal: Tmin + 42.5° C q 30 min	5-yr LC 24% 5-yr OS 0%	5-yr LC 69% 5-yr OS 53%	Yes Yes
***Perez*[101]**											
Miscellaneous superficial	Multicenter	218	107	111	32 Gy	8	4 wk	8	Goal: 42.5° C q 1h BW	CR 28%	CR 32%	No
***Perez*[100]**											
Final report on Trial		236	117	119	32 Gy	8	4 wk	8	Goal: 42.5° C q 1h BW	CR total 30% CR for lesions <3 cm, 35%	CR total 32% CR for lesions <3 cm, 52%	No No
***Datta*[102]**											
Head and neck	Single institution	65	32	33	50 Gy + boost	25	5 wk	BW	Goal: 20 min at 42.5° C	CR 31% at 6 wk Disease-free survival difference	CR 55% at 6 wk	Yes No overall Yes, stage II-IV

Key Phase III Trials: Hyperthermia Combined with Chemotherapy

Tumor Type/ Location	Type of Trial	N	Chemotherapy	No. Cycles	Thermal Dose Goals/ Reported Data	Endpoints
***Colombo*[104]**						
Recurrent or primary superficial bladder	Multicenter	80	Mitomycin C	8 weekly + 4 monthly	42° C ± 0.2° C q 1h	23/41 recurrences in control arm vs. 6/42 in combined arm
***Issels*[105]**						
Localized high-risk soft tissue sarcoma	Multicenter	341	Etoposide, ifosfamide, doxorubicin	Neoadjuvant 4 cycles + 4 cycles after local therapy completed	42° C 60 min q 1h	Local progression with median 34-mo FU Combined arm 56/169 CT arm 76/172

BW, twice a week; BT, brachytherapy; CEM, cumulative equivalent minutes; CR, complete response; CT, chemotherapy; Fx, fractions; FU, follow-up; Gy, Gray; h, hour; HT, hyperthermia; LC, local control; min, minutes; mo, months; No., number; NR, no response; OS, overall survival; PR, partial response; q, every; RR, relative risk; RT, radiation therapy; Rx, treatment; surv, survival; T, temperature; Tmin, minimum temperature; TTLTP, time to local tumor progression; Tx, treatment; wk, weeks; yr, year.

*Patients also received chemotherapy.

Clinical trials: hyperthermia in combination with chemotherapy

TABLE 28.1 Interaction of Heat and Chemotherapeutic Agents

Effect	Drug
Potentiated by heat	Melphalan
	Cyclophosphamide
	BCNU
	Cis-DDP
	Mitomycin C
	Bleomycin
	Vincristine
Unaffected by heat	Hydroxyurea
	Methotrexate
	Vinblastine
Complex interaction	Doxorubicin

BCNU, bischloroethylnitrosourea; Cis-DDP, *cis*-diamminedichloroplatinum.

From Kano E. Hyperthermia and drugs. In: Overgaard J, ed. *Hyperthermic Oncology*. London: Taylor & Francis, 1985:277–282, with permission.

Several possible mechanisms that underlie the interaction of heat with chemotherapeutic drugs *in vivo*:

(1) increased drug uptake and/or retention in cells

(2) increased DNA damage and inhibition of repair processes

(3) increased oxygen radical formation

(4) increased vascular delivery and tumor penetration

Phase III clinical trials: hyperthermia in combination with chemotherapy

- Enhancement of efficacy of both radiation and chemotherapy by heating is likely to involve overlapping mechanisms
- *In vitro* data reveal the potential for enhanced chemosensitization for several chemotherapeutic agents by increased temperature, even of only 1 to 2°C
- Hypoxic cell sensitizer have been shown to synergize with heat

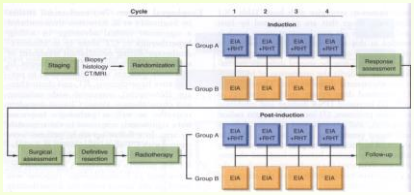
Clinical trials: hyperthermia in combination with chemotherapy

- Example 1: Esophageal cancer – two randomized studies by Sugimachi at al.
- Preoperative CT+HT vs. CT+HT+RT
  - CRs and pathologic responses significantly improved in trimodality arm
- Preoperative CT alone vs. CT+HT
  - Significant improvement in histopathologic response: 19 vs. 41%

Phase III clinical trials: hyperthermia in combination with chemotherapy

- Example 2: High-risk soft tissue sarcoma – randomized trials by Issels et al.
- Heating the tumor and the surrounding area (i.e., deep regional or part-body heating at a range between 40° to 43° C) during chemotherapy can significantly improve tumor control, including those in the extremities
- Demonstrated that non-uniform heating (varied 1 to 3oC across the tumor) can very successful

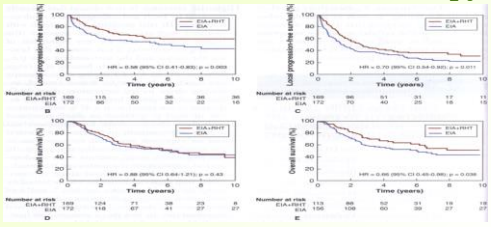
Phase III clinical trials: hyperthermia in combination with chemotherapy



EIA = etoposide +ifosfamide +doxorubicin

- Phase III trial in patients with high-risk sarcomas: study design

Phase III clinical trials: hyperthermia in combination with chemotherapy



Phase III trial in patients with high-risk sarcomas:

(B) Kaplan-Meier estimates of local progression-free survival, (C) disease-free survival, (D) overall survival in all patients randomly allocated treatment, and (E) overall survival in the per-protocol-induction population.

Hyperthermia with chemotherapy: thermosensitive liposomes

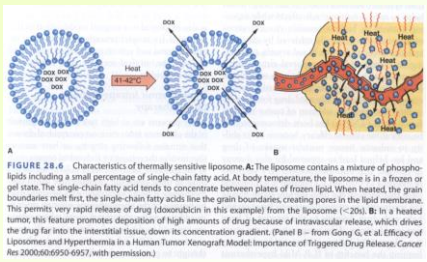


FIGURE 28.6 Characteristics of thermally sensitive liposome. **A:** The liposome contains a mixture of phospholipids including a small percentage of single-chain fatty acid. At body temperature, the liposome is in a frozen or gel state. The single-chain fatty acid tends to concentrate between plates of frozen lipid. When heated, the grain boundaries melt first, the single-chain fatty acids line the grain boundaries, creating pores in the lipid membrane. This permits very rapid release of drug (doxorubicin in this example) from the liposome (<20s). **B:** In a heated tumor, this feature promotes deposition of high amounts of drug because of intravascular release, which drives the drug far into the interstitial tissue, down its concentration gradient. (Panel B – from Gong G, et al. Efficacy of Liposomes and Hyperthermia in a Human Tumor Xenograft Model: Importance of Triggered Drug Release. *Cancer Res* 2000;60:6950-6957, with permission.)

Liposomes, sphere-shaped artificially created vesicles consisting of one or more phospholipid bilayers, were first described in the mid-60s.

Hyperthermia with chemotherapy: thermosensitive liposomes

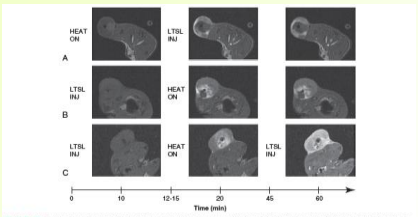


Figure 21-10 Example of monitoring drug delivery in real time, using liposomes containing an MR contrast agent ($MnSO_4$) and doxorubicin. Calibration studies showed that the change in T1 relaxation time, induced by the Mn^{++}, is linearly proportional to drug concentration, in vivo. HT is delivered to the tumor using a catheter containing circulating hot water at the center of the tumor (*shows as a dark spot near the center of each tumor*). **A**, When HT is administered, prior to and during drug administration, drug deposition is highest at the periphery of the tumor. **B**, When drug is administered first, followed by HT, the drug accumulates around the catheter, yielding a centralized drug deposition pattern. **C**, When drug dosing is split in half and given before HT and after HT has started, a more uniform drug deposition pattern is seen. Interestingly, the peripheral drug delivery pattern was most efficacious. LTSL, low-temperature-sensitive liposome.
Data from Ponce AM, Viglianti BL, Yu D, et al. Magnetic resonance imaging of temperature-sensitive liposome release: drug dose painting and antitumor effects. J Natl Cancer Inst 99(1):53-63, 2007.

Hyperthermia with chemotherapy

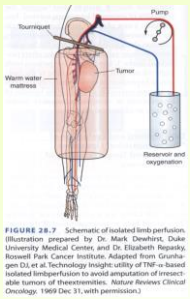


FIGURE 28.7 Schematic of isolated limb perfusion. (Illustration prepared by Dr. Mark Dewhirst, Duke University Medical Center, and Dr. Elizabeth Repasky, Roswell Park Cancer Institute. Adapted from Grunhagen DJ, et al. Technology Insight: utility of TNF-α-based isolated limbperfusion to avoid amputation of irresectable tumors of theextremities. *Nature Reviews Clinical Oncology*. 1969 Dec 31, with permission.)

- Isolated limb perfusion technique aims to avoid amputation of limb containing bulky tumors or multiple small tumors
- Regional drug concentration can be increased 15 to 25 times compared to systemic administration
- Temperature is kept at only 39 to 40ºC to avoid toxicities
- Therapy approved in Europe

Methods of producing hyperthermia

- Almost all local heating is currently delivered by
  - Microwave (100-MHz to 3-GHz)
  - Radiofrequency (500-kHz to 15-MHz)
  - Ultrasound (300-kHz to 2-MHz)
- Other techniques are either little used or in the developmental stage: radiofrequency inductively coupled, ferromagnetic seeds and nanoparticles, lasers

Methods of producing hyperthermia

- Several approaches to whole body hyperthermia
- Thermal conduction (surface heating): heated circulating water suits, heating blankets, and hot wax baths
- Extracorporeal induction: induced by heating blood during extracorporeal circulation (for example, venous perfusion WBH)
- Radiant heat or microwave radiation: the power absorption patterns are nonuniform, but redistribution of the thermal energy is rapid via the circulatory system

Clinical thermometry

- A major limitation of hyperthermia is the lack of detailed information available to guide hyperthermia
- Thus far use invasive thermometry is the standard
- A number of non-invasive thermometry techniques are under investigation to allow improved patient comfort and control of temperature distributions:
  - Infrared thermography
  - Fiberoptic sensors
  - Computed tomography, and magnetic resonance thermal imaging (MRTI)

Tumor ablation

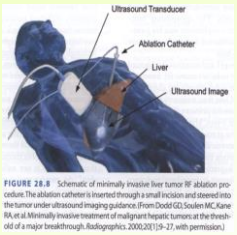


FIGURE 28.8 Schematic of minimally invasive liver tumor RF ablation procedure. The ablation catheter is inserted through a small incision and steered into the tumor under ultrasound imaging guidance. (From Dodd GD, Soulen MC, Kane RA, et al. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics. 2000;20[1]:9–27, with permission.)

- Tumors are heated for short intervals at high temperatures between 50° and 100° C to thermally "ablate" nodules
- At 50°C, it takes a few minutes to kill cells; above 60°C it takes only seconds
- There are now clinical trials in place in which thermal ablation is being combined with more traditional applications of hyperthermia to improve drug delivery through the use of thermosensitive liposomes at the margins of ablated tumors

Summary

- Hyperthermia has both additive and sensitizing effects in combination with radiation therapy
- Several phase III randomized clinical trials have demonstrated a clear and significant benefits of HT as adjuvant therapy
- With more understanding of biological mechanisms, as well as improved methods of heating and temperature monitoring, it should be possible to increase clinical TER values up to 2-4 (observable in animal tumors)