Biological, Physical, and Clinical Aspects of Hyperthermia

Survey of Clinical Radiation Therapy

Lecture 11-03-2014

Outline

- Introduction
- Biological principles of response to hyperthermia
- Delivery methods
- Thermometry
- Clinical aspects
- Summary

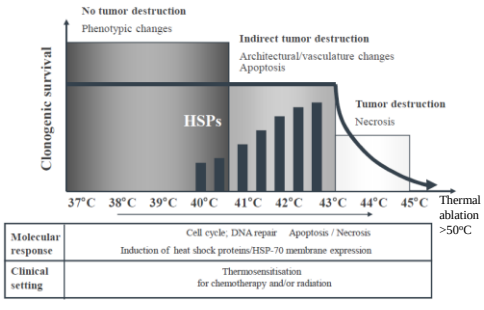
Introduction

- Heat was used in many cultures for treatment of 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

Introduction

- 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

Cellular and molecular events at elevated temperatures



Cellular and molecular events at elevated temperatures

- At the cellular level:
  - Slowing down or even blocking DNA replication
  - Inhibition of cellular repair mechanisms
  - Denaturation of proteins
  - Triggering of programmed cell death or apoptosis
- Changes in tissue physiology:
  - The microcirculation of the tumor, vascular permeability and hence the oxygenation; inhibition of angiogenesis
  - Stimulation of the immune system with observed increases in natural killer cell activity
- All of these events can significantly disrupt a tumor cell's capacity to divide, ultimately leading to shrinkage of tumors

Cellular response to heat

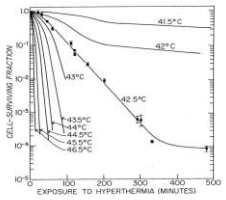


Figure 28.1. Survival curves for mammalian cells in culture (Chinese hamster ovary line) heated at different temperatures for varying lengths of time. (Adapted from Dewey WC, Hopwood LE, Sapareto LA, Gerweck LE: Cellular responses to combinations of hyperthermia and radiation. Radiology 123: 463–474,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

- There is great variability in genetically determined heat sensitivity of tumor cells:
  - Heat-resistant variants of B16 melanoma cells and of a radiation-induced fibrosarcoma (RIF-1) have been isolated and characterized

Biological aspects of hyperthermia vs. radiation

- Hyperthermia induces effects in both the nucleus and cytoplasm
- Killing is associated with degradation or denaturation of proteins
  - Radiation kills cells primarily through DNA damage
- Although the intermediate steps may be different, the ultimate cytotoxic effect of both heat and radiation is at the DNA level

Biological aspects of hyperthermia vs. radiation

- In organized tissues heat damage occurs more rapidly than radiation damage, because differentiated cells are killed as well as dividing cells
- 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

Hyperthermia and radiotherapy

- Hyperthermia is considered to be one of the most potent radiosensitizers
- Cells low in oxygen and pH range or in S-phase, as is often the case for cancers, are relatively radio-resistant – these are the cells most sensitive to hyperthermia
- Hyperthermia increases cytotoxic radiation effects by interfering with the cellular repair system as a result of the denaturing of the DNA

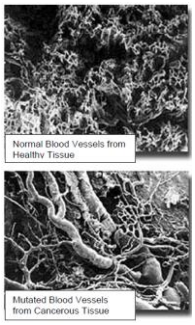
Hyperthermia and chemotherapy

- There is clinical evidence that heat increases killing of cells by direct thermal toxicity and shows thermal enhancement of drug efficacy
- This is because hyperthermia is able to increase cell membrane permeability, which is favorable for the penetration of chemotherapeutic drugs into tissues and absorption by the tumor
- Hyperthermia selectively increases the size of pores in endothelial cells, conduits of the drug in tumor vessels, while it does not cause this effect in normal tissues

Cell sensitivity to hyperthermia

- 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

Tumor blood supply



- As cancer cells multiply they can outgrow the capacity of their existing blood vessels to supply enough oxygen and nutrients
- In response, malignant tumors stimulate growth of additional blood vessels
- Because of this irregular blood vessel structure and rapid tumor growth, there are often large areas in tumors where the blood supply is deficient

Modes of hyperthermia application by target volume

- Localized hyperthermia - heat is applied to a small area restricted to the tumor
- Regional hyperthermia - attempts to heat moderately large volumes, such as the thorax or pelvis, including the cancerous region as well as surrounding healthy tissue
- Whole-body hyperthermia - raises the temperature of the entire body up to a fever-range temperature of 39.5°C (moderate hyperthermia) for 4-8 hours or to nearly 42°C for 1-2 hours
  - The tolerance of liver and brain tissue limits the T_{max}

Methods of Producing Local-Regional 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 Local-Regional Hyperthermia

Heating Techniques	Advantages	Disadvantages	Application (from the literature)	Commer. Availability
Microwaves	Technology very advanced. Heating of large volumes theoretically possible. Multiple applicators, coherent or incoherent, can be used. Specialized antennas for heating from body cavities have been developed. Skin cooling feasible. Interstitial use has been demonstrated	Heating not localized at depth; limited penetration at high frequencies. Possible adverse effects on personnel. Shielding of treatment rooms required, except at medically reserved frequencies (e.g., 915 MHz). Thermometry requires noninteracting probes. Temperature distributions subject to variations in local blood flow. Commercial antennas available are of fixed length. Depth of tissue implant alters specific absorption rate pattern.	Surface or near-surface lesions. Lesions on breast, chest wall, extremities (external applicators). Bladder, prostate, esophagus cervix, brain, head and neck with specialized or interstitial applicators	USA—yes Japan—yes Europe—yes
Radio-frequency (direct current or capacitive coupling)	Equipment relatively simple. No special shielding required. Large volumes may be heated. Heating of deep-seated lesions sometimes possible. Interstitial use has been demonstrated. Electrodes not limited in size; insulation easily accomplished	Fat tissue may heat preferentially. Current flow subject to local electrical tissue characteristics. Temperature distribution additionally subject to blood flow variations. Heating regional with external applicators.	Large-surface tumors; lesions in extremities, lung, pancreas, liver, bladder. Interstitial applications: chest wall, head and neck, prostate, uterine cervical cancer.	USA—no Japan—yes Europe—?

Methods of Producing Local-Regional Hyperthermia

Heating Techniques	Advantages	Disadvantages	Application (from the literature)	Commercial Availability
Ultrasound Single transducers	Readily focuses in tissue. Heating possible to 5–10 cm depth with focused transducers. Dynamic systems have been demonstrated. Shielding not required, and no health hazards to In dynamic systems, effects of blood flow can be reduced by minimizing focal volume	No penetration of tissue-air interfaces. "Shadowing" by bone. Bone tends to heat preferentially. Patients may experience pain during treatment.	Surface lesions; head and neck, and lesions in extremities.	USA—no Japan—yes Europe—yes
Multiple transducers	Focusing and preferential heating to 20-cm depth has been demonstrated. Dynamic systems can heat larger volumes.	As for single transducers (above).	Brain, prostate, head and neck.	USA—no Japan—yes Europe—yes

Table 35.1Methods of Producing Local-Regional Hyperthermia
From: Cancer Medicine, 6th Edition, Chapter 35, Principles of Hyperthermia

Methods of producing 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

Toxicity of whole-body hyperthermia

- Typically large fluid losses require vigorous replacement
- Electrolyte abnormalities, decreases in platelet count, and prolongation of coagulation are common
- Elevation in liver function tests, reflecting mild liver necrosis; sometimes skeletal muscle necrosis
- The physiologic response includes an approximate doubling of cardiac output with an increase in pulse rate but little change in blood pressure
- Diarrhea, nausea, and vomiting, posthyperthermia fever, and reactivation of herpes simplex infections are frequently observed

Thermal tolerance

Survival studies with Chinese hamster ovary cells

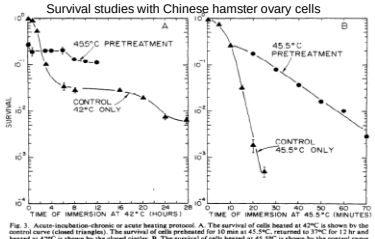


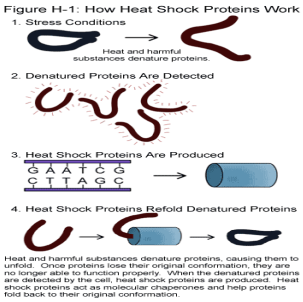
Fig. 3. Acute-incubation-chronic or acute heating protocol. A. The survival of cells heated at 42°C is shown by the control curve (closed triangles). The survival of cells preheated for 10 min at 45.5°C, returned to 37°C for 12 hr and heated at 42°C is shown by the closed circles. B. The survival of cells heated at 45.5°C is shown by the control curve (closed triangles). The survival of cells preheated for 10 min at 45.5°C, returned to 37°C for 12 hr and then heated at 45.5°C is shown by the closed circles. Error bars represent one standard error of the mean.

- Thermal tolerance is the effect of the development of a transient resistance to subsequent heating by an initial heat treatment

Thermal tolerance

- The appearance of certain proteins (identified by gel electrophoresis) tends to coincide with the development of thermal tolerance and their disappearance with the decay of thermal tolerance
- They have been named *heat-shock proteins* (though they are produced after treatment with other agents, e.g., arsenic and ethanol)
- Thermal tolerance must be taken into account when scheduling fractionated heat treatments of patients

Thermal tolerance



Thermometry

- A major limitation of hyperthermia is the lack of detailed information available to guide hyperthermia
- Thus far use invasive thermometry is the standard
  - Under local anesthesia, small needles or tubes with tiny thermometers are inserted into the treatment area. CT or ultrasound may be used to make sure the probes are properly positioned.
  - During WBH treatment, the esophageal, rectal, skin and ambient air temperatures are monitored at 10-minute intervals. Heart rate, respiratory rate, and cardiac rhythm are continuously monitored

Thermometry

- A number of non-invasive thermometry techniques are under investigation to allow both improved patient comfort and quantification of more complete temperature distributions
  - Infrared thermography
  - Fiberoptic sensors
  - Computed tomography, and magnetic resonance thermal imaging (MRTI)

Thermal dose

- Dose as "the measure of thermal effects" is a function of temperature, of time and of thermal sensitivity of target tissue that may depend on the presence of substrates and of drugs or previous damage
- There is no consensus on the best method of the thermal dose estimate
- Main difficulty: establishing dose-response relationship
  - In some cases there is little correlation between the thermal dose and clinical response

Thermal dose

- Thus far in clinical trials the dose-response correlation is best established for the radiant locoregional approaches
- The parameter: "cumulative equivalent minutes at 43°C" (CEM 43°C) calculated from the heat exposure time (t), the given temperature (T), and a constant (R) which is 0.5 when the temperature is higher than 43°C, and 0.25 if it is below 43°C, according to the formula

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

Thermal dose

- Dosimetric assessment of the absorption of EM energy by biological tissues is usually quantified in terms of the specific absorption rate (SAR), which is defined as the rate at which EM energy is absorbed by the tissue at a specific location per unit mass, in W/kg
- The SAR is determined by the incident EM waves, electrical and geometric characteristics of the irradiated subject and nearby objects; it is related to the internal electric field strength as well as to the electric conductivity and the density of tissues
- SAR values are of key importance when validating possible health hazards and setting safety standards

Clinical achievements

- Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy or other modalities
- Thus far it seems that locoregional hyperthermia methods may provide greater therapeutic gain than whole-body hyperthermia
- Three types of tumor: locally advanced cervical carcinoma, advanced neck disease of head and neck tumors, and glioblastoma showed a survival benefit

Clinical achievements

Table 1. Randomised trials on hyperthermia

Ref	Tumour site	Control	Experimental	Number of patients	Primary endpoint	Hyperthermia better (p<0·05)	Survival benefit
Local hyperthermia							
38	Head and neck (primary)	Radiotherapy	Radiotherapy and local hyperthermia	65	Response at 8 weeks	Yes	No
39	Melanoma (metastatic or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	68 (128 lesions)	Complete response (at 3 months)	Yes	No
40	Superficial (head and neck, breast, miscellaneous)	Radiotherapy	Radiotherapy and local hyperthermia	245	Initial response	possibly	No
41	Head and neck (N3 primary)	Radiotherapy	Radiotherapy and local hyperthermia (2–6 times)	44	Response (3 months)	Yes	Yes
42	Breast (advanced primary or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	307 (317 lesions)	Initial response	Yes	No
53	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	173 (240 lesions)	Best response	No	No
54	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	41 (44 lesions)	Initial response	No	No
55	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 2x local hyperthermia	Radiotherapy and 6x local hyperthermia	70 (179 lesions)	Initial response	No	No

Clinical achievements

Interstitial and endocavitary hyperthermia							
45	Superficial (head and neck, breast, melanoma, others)	Interstitial radiotherapy	Interstitial radiotherapy and interstitial hyperthermia	184	Best response	No	No
46	Glioblastoma	Radiotherapy and interstitial radiotherapy	Radiotherapy, interstitial radiotherapy, and interstitial hyperthermia	79	2-year survival	Yes	Yes
43	Rectum (T4, locally advanced)	Radiotherapy	Radiotherapy and endocavitary hyperthermia	115	Initial response	Yes	Yes
47	Oesophagus (stages I–IV, neoadjuvant)	Radiotherapy and chemotherapy	Radiotherapy, chemotherapy, and endocavitary hyperthermia	66	Histological complete response	Yes	Yes
48	Oesophagus (stage I–IV, neoadjuvant)	Chemotherapy	Chemotherapy and endocavitary hyperthermia	40	Initial response	Yes	No

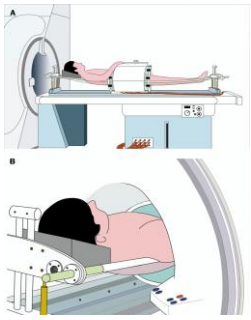
Clinical achievements

Perfusion hyperthermia							
49	Stomach (>T3, locally advanced)	Surgery	Surgery and hyperthermic intraperitoneal perfusion	82	5-year survival	Yes	Yes
50	Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	107	Disease-free survival	Yes	Yes
52	Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	832	Disease-free survival	No	No
Regional hyperthermia							
44	Cervix uteri (primary, stage III)	Radiotherapy	Radiotherapy and regional hyperthermia	40	Initial complete response	Yes	No
14	Primary or recurrent pelvic (cervix, rectum, bladder)	Radiotherapy	Radiotherapy and regional hyperthermia	361	Complete response rate, survival	Yes	Yes
Ongoing	Rectum (≥T3/4)	Radiotherapy and chemotherapy	Radiotherapy, chemotherapy, and regional hyperthermia	>150	Disease-free survival		
Ongoing	Soft-tissue sarcoma (high risk)	Chemotherapy	Chemotherapy and regional hyperthermia	>150	Disease-free survival		

Technological innovations in radiofrequency hyperthermia

- Recent development of "hybrid-systems" where an applicator for regional hyperthermia is implemented into an MR-tomograph
  - The proton-resonance frequency shift (PFS) method is used to perform reliable online thermometry in tumors (pelvis and extremities)
  - Enables online temperature monitoring, and an improved treatment regulation
  - Systems are already under evaluation in a number of hyperthermia centers worldwide, having installed the Sigma-Eye applicator of the BSD-system into an 0.2 Tesla (Munich) or 1.5 Tesla (Berlin, Durham) MR-tomograph

Technological innovations in radiofrequency hyperthermia



- (a) Hybrid system (installed at the Charité Medical Center, Berlin, Germany) with positioning system for the Sigma-Eye applicator (BSD Medical, Salt Lake City, USA) located in the back (with patient) of a tunnel-like MRT (Symphony 1.5 T, Siemens, Erlangen, Germany). The elliptical applicator can be moved on guide rails into the gantry after the patient has been positioned on the sling.
- (b) A front view of the MRT, also used for conventional diagnostic imaging

Hyperthermia approaches under investigation

- Novel interstitial ("corpuscular") technologies
- In *magnetic fluid hyperthermia* (MFH), the contact medium is consisting of magnetic nanoparticles which are directed into the tumor and heated within an alternating magnetic field (~ 100 kHz)
- Although the development of MFH goes back to the 1950's, first applicator systems only recently became commercially available

Hyperthermia approaches under investigation

- A new generation of *thermo-sensitive liposomes* has been developed which reliably enable the liberation of drugs into a heated tissue at predefined temperatures
  - Recent studies suggest that those technologies may largely improve the thermal control of hyperthermia-guided drug-targeting
- *Hyperthermia-induced gene therapy* (HIGT) is based on the principle that heat application and other mediators of cellular stress are suited to induce the expression of some genes promoting anti-cancer effect

Exclusion criteria for using hyperthermia

- Locoregional deep hyperthermia cannot be used for patients with electronic cardiac pacemakers since it is not possible to guarantee that the electronics of the pacemaker will not be destroyed, resulting in functional disruptions
- Patients who have tumors in the direct vicinity of metal implants such as joint prostheses, braces, etc., are difficult to treat since the metals can heat up excessively under the influence of hyperthermia

Summary

- Hyperthermia is an emerging therapy in oncology
- When combined with radiotherapy and/or chemotherapy may provide useful local supportive or palliative effects
- The underlying mechanisms, the possible risks and safety issues, and the limits of its applications are still not clearly understood
- The clinical exploitation requires
  - Improvements in the equipment used for performing, monitoring and planning hyperthermic treatments
  - Refinement of appropriate thermal dose goal standards

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