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

- 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

- 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
Methods of Producing Local-Regional Hyperthermia

- **Advantages**
  - 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

- **Disadvantages**
  - Remaining tumor growth is often due to insufﬁcient oxygen and nutrient supply
  - In response, malignant tumors stimulates 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

Methods of producing whole-body hyperthermia

- **Advantages**
  - 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

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

Methods of Producing Local-Regional Hyperthermia

| Heating Techniques | Advantages | Disadvantages | Application (from the literature) | Comment Availability
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<tr>
<td>Ultrasound Single transducers</td>
<td>Readily focuses in tissue. Heating possible to 5–10 cm depth with focused transducers. Dynamic systems have been demonstrated. Shading not required, and no health hazards to the patient.</td>
<td>No penetration of tissue-air interface. &quot;Shadows&quot; by bones, head and neck, and lesions in extremities.</td>
<td>Surface lesions: head, face, and neck (interstitial).</td>
<td>USA—no Japan—yes Europe—yes.</td>
</tr>
</tbody>
</table>

| Methods of Producing Local-Regional Hyperthermia | Advantages | Disadvantages | Application (from the literature) | Comment Availability
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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

- 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

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

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

$$ CEM \ 43^\circ \ C = R^t (43 - T) $$

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>
<thead>
<tr>
<th>Table 1. Randomized trials on hyperthermia</th>
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<tr>
<td>Type of tumor site</td>
<td>Control</td>
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<tr>
<td>--------------------</td>
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<tr>
<td>21</td>
<td>Head and neck cancer (oral, tonsil, larynx)</td>
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Clinical achievements

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<tr>
<th>Regional Hyperthermia</th>
<th>Local Hyperthermia</th>
<th>System</th>
<th>Temperature</th>
<th>Survival</th>
<th>Results</th>
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<tr>
<td>Prostate, rectum</td>
<td>Rectal, anal canal,</td>
<td>applicator</td>
<td>45°C</td>
<td>5-year survival</td>
<td>Yes</td>
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<tr>
<td>Bladder, pelvic</td>
<td>bladder</td>
<td>applicator</td>
<td>45°C</td>
<td>5-year survival</td>
<td>Yes</td>
</tr>
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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

References

- Cancer Medicine, 6th Edition, Chapter 35, Principles of Hyperthermia
- J. van der Zee, Heating the patient: a promising approach?, Annals of Oncology 13, 2002