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Hyperthermia – description of a method and a review of clinical applications

Adam Chicheł, Janusz Skowronek, Magda Kubaszewska, Marek Kanikowski

Department of Brachytherapy, Greatpoland Cancer Center, Poznań, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

The aim of this paper is to give a concise description of hyperthermia and a brief review of its clinical applications. Hyperthermia (HT, thermal therapy) is thought to be one of the cancer therapies and is considered to be an artificial way of increasing the body tissue temperature by delivering heat obtained from external sources to destroy cancerous cells or prevent their further growth. The first principles of hyperthermic biology are presented. The phenomena of thermotolerance and radiosensitization are briefly described, as well as the concept of thermal dose delivered to the tissues.

Three main clinical applications of HT are presented. They include local, regional or part-body HT and whole-body HT that deliver heat to localized, advanced or deep-seated and disseminated malignancies, respectively, depending on location, depth and staging of the tumour. Energies used to apply heat to the tumour include microwaves, radiofrequency energy, ultrasound, infrared radiators and different kinds of hot sources (hot water, ferromagnetic seeds, nanoparticles, resistive implants). General indications for each HT subtype and possible combinations of HT with other cancer treatment modalities are presented.

Substantially, HT is used as an adjuvant therapy and in such a role it is being evaluated in many clinical randomized trials throughout the scientific medical centres. Their first preliminary results are already available, but still time is needed to produce firm conclusions and strict indications for hyperthermia treatment.

Key words **hyperthermia • cancer • method of treatment • clinical applications • heating techniques**

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Author's address: Janusz Skowronek, Department of Brachytherapy, Greatpoland Cancer Center, Garbary 15 Str., 61-866 Poznań, Poland, e-mail: janusz.skowronek@wco.pl

Definition of Hyperthermia

Hyperthermia (HT, thermal therapy, thermotherapy) is thought to be one of the cancer therapies amongst surgery, radiation therapy, chemotherapy, gene and immunotherapy. It is a natural or artificial phenomenon that involves increasing the temperature of the body or a particular region of it over the threshold temperature set at a particular moment by the thermoregulation system of an organism [1–3]. In the field of oncology HT is considered to be an artificial way of increasing the body tissue temperature by delivering heat obtained from external sources to destroy cancerous cells or prevent their further growth. Hyperthermia is mostly identified with a range of temperatures from 40 to 48°C or similar maintained at a treated site for a period of one hour or more [4–7]. Because of the results that high temperature may produce in tissues, one can refer to use of temperatures >50°C as coagulation, 60 to 90°C as thermal ablation, >200°C as charring [2,8].

First Principles of Hyperthermia Biology

High temperatures, as has been shown in many research studies [6], cause direct damage to cancerous cells themselves and also sensitize them to other treatment modalities (radiotherapy, chemotherapy, gene therapy and immunotherapy) with usually minimal or no injury to normal tissues [4,7,9–11]. Accordingly, HT is mainly used as an adjuvant therapy, not as a sole one [2,5,9]. For instance, applying HT weekly, concomitantly with radiation, results in faster tumour regression rate than radiation alone [12] (Figure 1). HT kills cells itself, implicates radiotherapy by inducing reoxygenation, increases delivery of liposomally encapsulated drugs [11,13] and macromolecules such as monoclonal antibodies or polymeric peptides, enhances cellular effects of chemotherapeutics and augments immune reactions against the tumour due to thermotolerance mediated by heat shock proteins (HSPs) [14–16].

Thermotolerance is a general phenomenon referred to as transient resistance to additional heat stress, thus making it impractical to apply two different HT sessions with an interval shorter than 48–72 hours, until the resistance decays to a negligible level [4,7,10].

On the other hand, thermotolerance does not really affect radiosensitization [17] and, what is crucial, may be avoided by exposure of the tumour to temperatures over 43°C (optionally, step-down heating). The latter, unfortunately, is quite difficult to achieve in the clinic [4,10].

Killing cells depends on the duration of heating and high temperature levels achieved during particular treatment sessions. The higher the temperature and the longer time that heat is delivered to the tumour, the stronger the lethal effect and the less thermotolerance is induced in it. Briefly, protein is a predominant target of HT [9,18]. Denaturating intracellular proteins destabilize cellular membranes, cytoskeleton, enzymes, signal transduction, macromolecular synthesis and cell nucleus (by interfering with DNA repair systems). Temperature elevated above the physiological level results in changes in blood flow, vascular permeability and tumour oxygenation [19,20]. The final effect of the above is necrotic or apoptotic death of preheated cells or their sensitization to ionizing radiation or chemotherapy [5,10,18,21]. It is worth noticing that cells in the S-phase are the most sensitive to thermal therapy and the least sensitive to radiation [4,7].

Environmental and vascular conditions are important as well. Damage to cancerous cells is promoted by chronic hypoxia, decreased pH, deprivation of nutrients and poor cooling, which are caused by pathological microvasculature within the tumor [7]. In general, the mentioned conditions are not seen in normal tissues which are not seriously affected by thermal treatment (Figure 2). On the basis of an Arrhenius plot (an isoeffect plot presenting the logarithm of the slope of cell survival curves as a function of temperature) one can state that there is a breakpoint, estimated to be about 43°C, over which increasing the temperature by 1°C results in doubled cellular death rate [4,7,10].

Thermal Dose

As for now CEM 43°C T90 (cumulative equivalent minutes at a standard targeted treatment temperature of 43°C obtained within 90% of the tumour volume) appears to be the most useful dosimetric parameter in clinical research [1,22]. 10 CEM 43°C T90 is suggested as a goal of the treatment. This can be explained by the fact that heating a particular tumour and delivering at least 43°C to 90% of its volume for cumulative (in multiple treatments) ⩾10 minutes corresponds to doubling of the probability for complete response and duration of response to hyperthermia and radiotherapy versus radiotherapy alone [23]. Simplifying

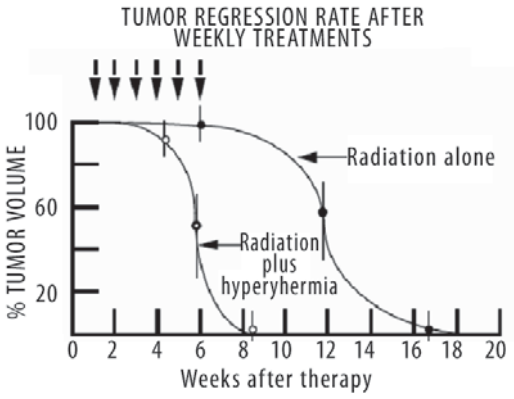

Figure 1. Hyperthermia added to radiation therapy and its enhancing influence on tumour regression in an example of malignant melanoma [12].

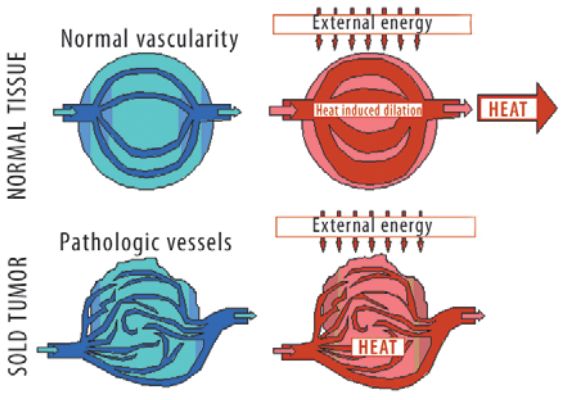

Figure 2. Mechanism of overheating the tumour. In normal tissue (above) blood vessels dilate when physiologically or artificially heated, which causes increase in blood flow through the region and decreases its temperature. In the tumour (below), on the other hand, pathologic vessels are not able to dilate, some of them collapse, so delivered heat is not reduced by blood flow and intratumoural temperature increases.

Table 1. Subtypes of hyperthermia, examples of clinical applications and types of energy delivered to tumours.

Types of hyperthermia	Type/site of tumour	Clinical applications	Types of energy/equipment
Local HT: – superficial – intracavital – intraluminal – interstitial	Superficial tumours Intracavital tumours Intraluminal tumours Intracranial tumours	Head & neck cancers Locally advanced or recurrent breast cancer Malignant gliomas Rectal cancer Oesophageal cancer Soft tissue sarcomas	Microwaves (MW) Radiofrequency (RF) Ultrasound (US) **Hot sources:** – Hot water perfusion – Resistive wire implants – Ferromagnetic implants – Nanoparticles
Regional/Part-body HT: – abdominal – pelvic – limbs	Deep seated tumours Locally advanced tumours	Cervical cancer Rectal cancer Bladder cancer Prostate cancer Soft tissue sarcoma Ovarian cancer Mesothelioma Peritoneal carcinomatosis	
Whole-body HT	Disseminated/metastatic diseases	Malignant melanoma Recurrent soft tissue sarcomas Ovarian cancer	Infrared radiators Hot water blankets Thermal chambers

the above, the higher the minimum temperatures obtained in the tumour, the better the clinical outcome achieved [24–26]. RTOG guidelines in force precisely describe the rules of thermometry necessary for CEM calculations and assurance of hyperthermia quality [27]. By definition, thermometry in tumours is invasive, and thus connected with particular complications.

Some ongoing investigations are targeted at developing magnetic resonance imaging (MRI) as a tool of non-invasive thermometry [28–31].

Methods of Hyperthermia

There appear to be three main clinical methods of high temperature application depending on location, depth and staging of the tumour. Local, regional and whole-body hyperthermia deliver heat to localized, advanced or deep seated and disseminated malignancies, respectively [1,5,6,9,11,32–34] (see Table 1). Energies used to apply heat to the tumour include microwaves (in the range of wavelengths from 433 to 2450MHz), radiofrequency (ranging from

Figure 3. An example of equipment for superficial and interstitial hyperthermia (BSD 500 hyperthermia system) operating on microwaves of 915MHz.

100KHz to 150MHz), ultrasound, hot water perfusion (tubes, blankets), resistive wire implants, ferromagnetic seeds, nanoparticles, and infrared radiators [4,9,35] (Figure 3).

Local Hyperthermia

Local hyperthermia is dedicated to rather small tumours (≤3 cm up to 5–6 cm in the longest diameter) [4,5,36–38] located superficially or within an accessible body cavity such as the rectum or oesophagus. Superficial, interstitial, intraluminal or intracavital applicators can be applied and, most commonly, microwaves, radio waves or ultrasound are used to deliver heat to the tumours. Local techniques enable heating of small cancerous areas with sufficient sparing of normal tissues. Prevention of side effects during hyperthermia sessions consists of concomitant cooling using water boluses whose purpose is to maintain the temperature of the skin at a level of about 37°C and to ensure electromagnetic coupling of the applicator to the tissue. This results in less blistering and rare burning of the skin.

Tumours located in the skin or just below can be heated with superficial applicators or antennas (accessible in different forms of waveguide, spiral, current sheet or compact applicators, available commercially) emitting a particular type of energy, placed directly in or near the area of interest (Figures 4,5). To gather necessary information about gained temperature, implantation of tubes or needles into anaesthetized tumour tissue is necessary. They enable the insertion of tiny thermometers (e.g. Bowman or fibre optic probes) for temperature measurements. Proper positioning is sometimes assured by ultrasonography or computed tomography [6].

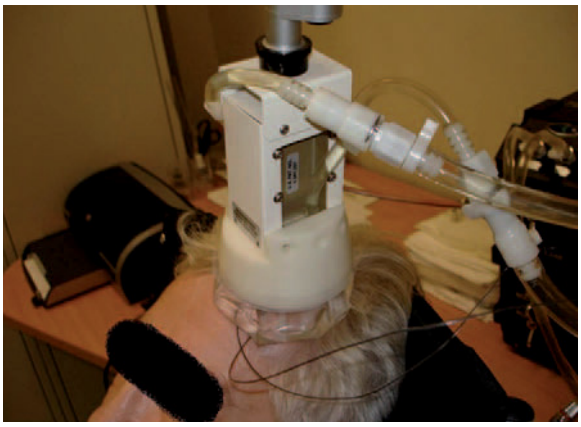

Figure 4. Superficial MW hyperthermia of malignant melanoma of the skin. Hyperthermia used concomitantly with HDR brachytherapy. The small MA 151 applicator is used, BSD 500 hyperthermia system.

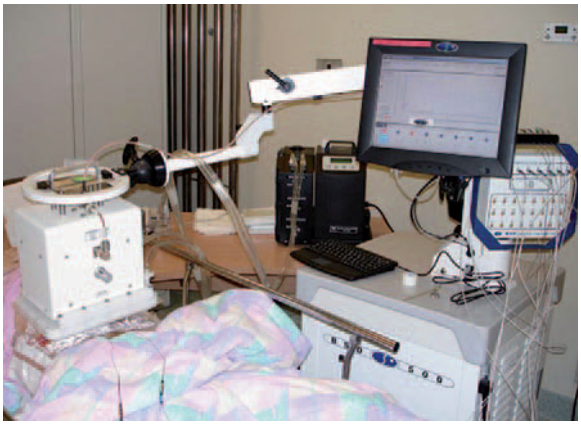

Figure 5. Superficial hyperthermia in management of skin metastases of ovarian cancer, concomitant with chemotherapy. The largest MA 120 superficial applicator is used, BSD 500 hyperthermia system.

Natural orifices of human body cavities can be the way of intracavital or intraluminal hyperthermia applications delivering heat directly into the prostate (urethra, rectum), rectal cancer, vagina, cervix or oesophagus.

Finally, there is a technique for heating tumours interstitially. It is dedicated to the spectrum of tumours able to be treated with brachytherapy

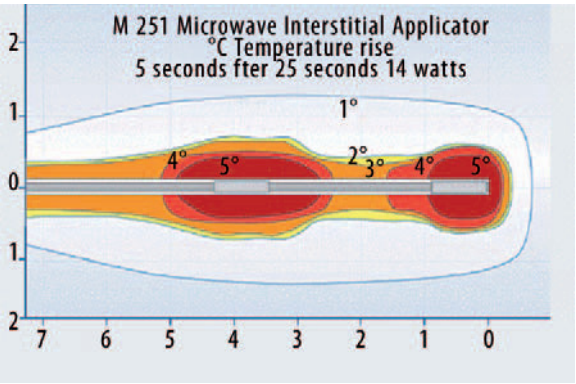

Figure 6. Interstitial applicators for MW hyperthermia used in BSD 500 systems. The distal 4.5 cm are used for heating the tissues.

(head and neck tumours, prostate cancer, breast cancer or brain malignancies). Tiny microwave antennas, radiofrequency electrodes, ultrasound transducers, heat sources or laser fibres are inserted into the tumour tissue via brachytherapy applicators to be used for heating up to 2 hours before or just immediately after radiation (Figure 6). Like brachytherapy, interstitial hyperthermia is an invasive procedure and is suitable for lesions not larger than about 5cm. The method demands an array of applicators to be implanted under local or, sometimes, general anaesthesia (Figure 7). Some of them are used for inserting hyperthermia devices, while the rest are necessary for interstitial thermometry, especially between the antennas (for temperature mapping and to avoid hot spots). Some authors put thermometers on the skin above the tumour, too [9]. The distance between antennas should not exceed 1 to 2cm because of the steep radial decrease in power deposition and vascular perfusion that interacts with the temperature rise in the heated tissue.

Among interstitial hyperthermia techniques, radiofrequency ablation should be noted as well. Thermoablation uses radio waves to raise temperature within the tumour to over 50°C for more than 4 to 6 minutes or for >512 CEM 43°C, and causes vascular stasis, cellular coagulation and tissue necrosis. This method is able to destroy small focal tumours located within the liver, lung, kidney or bones [8,39–43].

There is also a new cancer therapy using magnetic nanoparticles for thermal treatment. In this method nanoparticles of iron oxide are injected directly into the tumour tissue and subsequently heated using a magnetic field. This provides an opportunity to heat tumours situated in deep body regions such as the skull (recurrent glioblastoma) or pelvis (prostate and cervical carcinoma) [35].

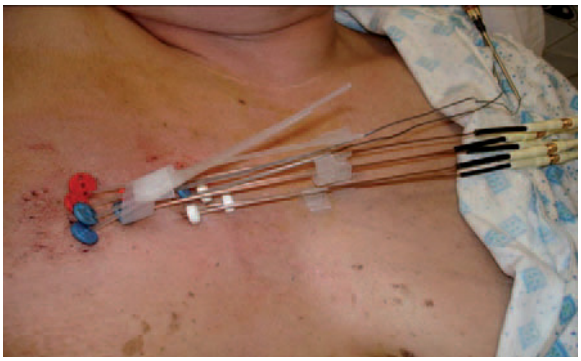

Figure 7. Interstitial hyperthermia in a radical treatment of right breast cancer – concomitantly with HDR brachytherapy boost after teleradiotherapy. Five hyperthermia applicators and two thermometers are inserted into the elastic breast applicators.

Regional Hyperthermia

Regional or part-body hyperthermia is a term for heating large parts of the body, e.g. abdominal cavity, particular organs or limbs. Most often it is devoted to treating advanced tumours situated in the major and minor pelvis, abdomen (cervical, prostate, bladder, colorectal and ovarian carcinomas) or thighs (soft tissue sarcomas). Three main approaches can be listed: deep-seated tumours heated with external applicators, limbs or organs heated by means of thermal perfusion, and continuous hyperthermic peritoneal perfusion (CHPP).

Common external applicators consist of coherent arrays of dipole antenna pairs positioned in a ring pattern around the patient. The antennas emit microwave or radiofrequency energy to be focused in a cancerously altered part of the body. With such equipment selected anatomical regions can be heated up to 41–42°C and this temperature is limited by power deposition in surrounding tissues. Phase and amplitude of each antenna (radiating in a range of 70 to 150MHz) can be controlled in regard to generated SAR distribution. SAR (specific absorption rate) is a physical parameter used to describe the interaction between electromagnetic field and matter. Two other deep-heating methods involve capacitive and inductive techniques, both operating with radiofrequency sources [1,4,44,45]. In recent years researchers have made a lot of attempts to develop planning systems and treatment monitoring systems useful for deep regional hyperthermia, most often taking advantage of magnetic resonance tomography, which can be helpful in noninvasive recording of tissue temperature and perfusion [1,28,46–48].

Malignancies affecting arms or legs (e.g. melanoma) or some organs (liver, lung) can be treated with regional perfusion. The procedure consists in bypassing a large supplying artery of a limb or organ and a limb- or organ-draining vein in order to deliver heat to the drained blood in an extracorporeal way. This method brings less systemic side effects in comparison with whole-body hyperthermia and is often administered with concomitant chemotherapy in cases of limb melanomas, soft tissue sarcomas of extremities and liver malignancies [5,49–51].

Continuous hyperthermic peritoneal perfusion (CHPP) or, with the addition of chemotherapeutic agents, hyperthermic intraperitoneal chemotherapy (HIPEC) are treatment modalities used to deal with cancers disseminated within the abdominal cavity. There can be listed peritoneal carcinomatosis of unknown origin, multifocal ovarian or colorectal metastases, mesothelioma and stomach cancer. The therapeutic strategy consists of resection of the primary tumour and cytoreduction of its peritoneal metastases, as well as liver metastases, in some cases. CHHP or HIPEC is administered perioperatively, delivering warmed washing fluid (41.0–42.5°C) with or without anticancer drugs to the peritoneal layers [33,34,52–55].

Whole-Body Hyperthermia

Whole-body hyperthermia (WBH) is a chance for patients with metastatic disease such as melanoma, soft tissue sarcoma or ovarian cancer. Disseminated cancerous cells are thought to be destroyed or sensitized to drugs with high temperature of the whole organism. To achieve that aim (approximately 41.8–42.2°C) thermal chambers, hot water blankets or infrared radiators are used, concomitantly with prevention of temperature loss and electrolyte fluids restoration. Depending on subtype of WBH, patients demand general anaesthesia or deep sedation while heated up to 42.0°C for 60 minutes (extreme WBH) or to 39.5–41.0°C for 3 to 4 hours (moderate WBH), respectively. WBH offers the most homogeneous thermal distribution, but, on the other hand it is related to the greatest probability of complications (thermal stress to the heart, lungs, liver or brain). Most commonly transient diarrhoea, nausea and vomiting are observed [4,5,9,15,36,56–58]. It is worth noticing that using WBH in childhood refractory malignant solid tumours offers an increase in tumour sensitivity to chemotherapy and results in better outcome than standard therapeutic approaches [59].

Application of Hyperthermia Among Other Anticancer Treatment Modalities

Hyperthermia is rarely used as a single cancer treatment modality and is usually added to radiation therapy, chemotherapy or radiochemotherapy, and recently to gene and immunotherapy [4,5,7,9–11]. All the regimens have the status of scientific research or clinical trials focusing on the treatment of many types of cancer, especially those with poor outcome (melanoma, soft tissue sarcoma, head and neck cancers, malignancies of the brain, lung, breast, cervix, colon, bladder, oesophagus and liver) [1,5,6,9,11,32]. Some of them have already proved the efficacy of hyperthermia in combined treatment [5,6,9,11,60], but others have not [5,6,11]. As for now, hyperthermia added to radiotherapy in breast cancer, melanoma, glioblastoma, head and neck tumours and cervix cancer significantly improves response and survival [61–66].

HT delivered alone or in combination with other cancer treatment is generally well tolerated and, if the temperature does not exceed 44.0°C, rarely affects normal tissues. Higher thermal depositions can lead to blistering, burns, pain or necrosis. In case of perfusion techniques there may appear swelling of the heated tissue, ischaemia due to blood clots or bleeding. On the whole, thermal side effects are transient [1,5,9,11,67].

Currently, there are a variety of commercially available systems for hyperthermia produced by different companies or tested in scientific institutions. Despite the fact that there is a strong rationale for using HT in some clinical situations, there is still a lack of strict indications in which cases HT should be delivered obligatorily. Many clinical trials have to be closed and summarized to firmly state that hyperthermia is an effective, standard cancer treatment. At present, some studies have to focus on developing improved hyperthermia techniques and find solutions for the best combinations of concomitant therapies in the treatment of different types of cancer.

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