Hyperthermia in Cancer Treatment

RCT summary for professionals

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1. Abstract

Hyperthermia is a therapeutic procedure used to raise the body or local tissue temperature to about 41-43°C through the application of electromagnetic or ultrasound energy for a defined period of time to sensitize cells for additional therapies. It was introduced into clinical oncology practice several decades ago. Positive clinical results, mostly obtained in single institutions, resulted in clinical implementation albeit in a limited number of cancer centers worldwide. Hyperthermia is almost always used with other forms of cancer therapies as it provides a possibility for synergy with different actions of conventional therapies. Hyperthermia in combination with radiotherapy and/or chemotherapy results in higher response rates, accompanied by improved local tumor control rates, better palliative effects and/or better overall survival rates in selected cases of tumor types. Significant improvement in clinical outcome has been demonstrated for tumors of the bladder, breast, cervix, head and neck, and soft tissue sarcomas. In this article, background information on the biological rationale for the application of hyperthermia to human cancer treatment, an overview of technologies and a summary of clinical outcomes published since 2005 are provided.

**Keywords:** chemohyperthermia, continuous hyperthermic peritoneal perfusion, electromagnetic therapy, heated intraoperative intraperitoneal chemotherapy, hyperthermia, hyperthermic intraperitoneal chemotherapy, HIPEC, isolated limb infusion, thermal therapy, thermotherapy

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2. What is it?

2.1 Introduction

The tumoricidal properties of hyperthermia have been recognized since ancient times (Breasted, 1930). The first paper on hyperthermia was published by W. Bush in 1886. At the end of the 19th century William B. Coley used infections with bacteria and/or injections of bacterial extracts to induce fever for treating patients with cancer, now referred to as the Coley Toxin. Increased interest in the use of hyperthermia for the treatment of cancer developed in the 1960s, and various devices to produce either systemic hyperthermia or hyperthermia in selected parts of the body were developed. In the past 15 years new developments and technologies have transformed hyperthermia into a valuable therapy for certain tumor cases. However, today hyperthermia is not widely used and the three conventional therapeutic modalities (surgery, radio- and chemotherapy) dominate cancer treatments. What are the reasons for this, given its long history and evidence of promising results over the last decade? Initially, hyperthermia in oncology had many controversial results and as a consequence, ambivalence in the medical community. In addition, the incorrect use especially during the emergence of hyperthermia some 10 years ago or inadequate techniques to allow treatments to be reproduced in clinics may be responsible for its current limited acceptance. Technical challenges in treatment delivery, including difficulty achieving therapeutic temperatures for deep-seated tumors, have hindered the widespread use of hyperthermia (Hurwitz et al., 2011). The challenges for hyperthermia lie also in its relatively complicated practice as, despite its simple principle, the required permanent and intensive care from medical personnel takes a relatively long time in comparison to the radio- or chemotherapies. Hyperthermia today also lacks adequate treatment experience and long-range, comprehensive statistics. At this moment, most advances are being made on improving heating technology, thermometry, the development of hyperthermia treatment planning models and, most recently, drug targeting using thermosensitive drug-carriers such as nanoparticles (Cherukuri et al., 2010) and liposomes (Landon et al., 2011). The understanding of the biological effects involved is growing, i.e. heat-shock proteins, anti-cancer immune responses and the role of hyperthermia in hormone gene therapy. The positive results of most of the recent studies may explain the renewed enthusiasm for hyperthermia, which is reflected in the growing number of institutes interested in the application of hyperthermia. Currently, hyperthermia is available in clinical research centers and private clinics mainly in Austria, China, Germany, Italy, Japan, North America, Switzerland and The Netherlands.

2.2 Principles of hyperthermia

Various forms of thermal therapies are being used in the treatment of cancer. They are divided into hyperthermia, thermal ablation and cryoablation in accordance with the temperature range being used. Hyperthermia, also often called thermal therapy or thermotherapy, is a cancer treatment in which cancer tissue or the whole body is exposed to temperatures between 41-43°C through the application of electromagnetic energy for a defined period of time to damage and kill cancer cells. Above this temperature, heat has a direct cytotoxic effect on both normal and tumor cells and is referred to as thermal ablation.
Thermal ablation is using much higher temperatures of >45°C and will be reviewed elsewhere. Cryoablation or cryosurgery, using temperatures below minus 50°C is also defined within the category of thermal therapies even though it is part of a surgical intervention.

Hyperthermia causes numerous subtle changes in tissue physiology. An increase in temperature due to hyperthermia changes the microcirculation of the tumor and hence the oxygenation (Franckena and van der Zee, 2010). The oxygenation of the tissue is tightly connected to vascular permeability which is modified by hyperthermia (Song et al., 2001; Thrall et al., 2006). Also, increased temperature may slow down or even block DNA replication (Xu et al., 2007) or inhibits cellular repair mechanisms (Krawczyk et al., 2011), denature proteins, and inhibit angiogenesis (Dahl et al., 2008). Hyperthermia has been shown to induce heat-shock proteins (Ciocca et al., 2010; Jolescha et al., 2011) and stimulate the immune system (Calderwood et al., 2005; Dieing et al., 2007; Peer et al., 2010) with observed increases in natural killer cell activity (Dayanc et al., 2008). Lymphocytes, which are encountered in large numbers both in the blood as well as between the body cells, would be more reactive due to the increased temperature. Another potential harmful effect of hyperthermia is the triggering of programmed cell death or apoptosis in tumor cells (O’Neill et al., 1998; Arya et al., 2007). The effects of hyperthermia on cancer are thus pleiotropic and complex. All of these events can significantly disrupt a tumor cell’s capacity to divide, ultimately leading to shrinkage of tumors. The tissue injury caused by hyperthermia occurs in two distinct phases. The initial phase is direct heat injury that is predominantly determined by the total energy applied to the tumor, tumor biology, and tumor microenvironment (Nikfarjam et al., 2005a). The second phase is indirect injury after focal hyperthermia application, which produces a progression in tissue damage. This progressive injury may involve a balance of several factors including microvascular damage, ischemia reperfusion injury, induction of apoptosis, Kupffer cell activation, altered cytokine expression, and modulation of the immune response (Nikfarjam et al., 2005b; Torigoe et al., 2009). The effects of heat depend on tissue temperatures attained, determined by the total thermal energy applied, rate of removal of heat, and the specific thermal sensitivity of the tissue. In addition, the form, type and size of tissue and the homogeneity of temperature distribution can affect the denaturation of cellular and subcellular elements.

Hyperthermia can be applied using several methods. The most common method is to apply hyperthermia locally using electromagnetic energy to heat the tumors which may be located in various parts of the body. Local hyperthermia has been used extensively for superficial lymph nodes, prostate, and cutaneous or subcutaneous melanoma metastasis. Regional hyperthermia has been used primarily for recurrent or advanced breast cancer, advanced pelvic tumors and for sarcomas of the trunk or extremities. In general, hyperthermia can be used with all stages of cancer, although its current main use is with advanced solid tumors that are hardly operable or inoperable, as well as with recurrent tumors and metastases. Also where conventional therapy approaches (surgery, chemotherapy, radiation therapy) are not very likely to be successful, or have proven to be inadequate, hyperthermia has already been successfully used with some tumors including their metastases in different organs (see 3.2).
Today, hyperthermia is almost always used with other forms of cancer therapies as it provides a possibility for synergy with different actions of conventional therapies. The scientific basis for the use of hyperthermia as an adjunct for the treatment of cancer rests on several observations. Tumor cells that make deoxyribonucleic acid (DNA) in preparation for division and those that are acidic and poorly oxygenated tend to be resistant to radiation (Dewhirst et al., 2005). As a consequence, hyperthermia may make cancer cells more sensitive to radiation or harm other cancer cells that radiation cannot damage. The combination of chemotherapeutic agents and hyperthermia produces additive and synergetic killing effects on tumor cells as well (Ponce et al., 2006; Issels, 2008). These effects appear more dramatic at low pH. Heat can also potentiate the cytotoxic effect of a variety of chemotherapeutic agents.

2.3 Mechanisms of heating

Laboratory and clinical studies have documented multiple mechanisms of action for hyperthermia. A large number of different methods exist to apply active hyperthermia. To deliver the heat three fundamental processes exist: (1) thermal conduction of heat away from a source at higher temperature; (2) a combination of resistive and dielectric losses in tissue from an applied electromagnetic (EM) field; or (3) mechanical losses from molecular oscillations caused by an ultrasonic pressure wave.

2.3.1 Thermal conduction

In the simplest form of hyperthermia, tissue may be heated by circulating externally pre-heated blood through the tissue, by placing a heated surface (e.g. a water bolus pad) on the skin or in the body cavities, or by interstitially implanting hot sources in wires, needles, or catheters into the target tissue. It is generally not possible to heat well perfused, normal tissue more than 3 to 5 millimeters from a hot surface. Today, this technique is rarely used.

2.3.2 Electromagnetic power deposition

The electric properties of human tissues vary considerably. The primary mechanism of EM heating of tissue also varies with frequency. In the radiofrequency (RF) range (hundreds of kilohertz to a few megahertz), the alternating field induces a net movement of free electrons, and power deposition results from resistive (ohmic) losses caused by the electric currents in lossy tissue. At microwave (MW) frequencies (hundreds of megahertz to approximately ten gigahertz), the dielectric losses in tissue predominate and heating results primarily from friction caused by interactions between polar water molecules that rotate and oscillate to maintain alignment with the time-varying EM field. At higher frequencies, power is deposited more superficially, whereas lower frequencies provide deeper penetration. Lower RF frequencies penetrate well but affect large regions of the body, whereas higher MW frequencies may be localized effectively in tumor-sized tissue volumes. Despite the large numbers of heating methods, presently the electromagnetic methods dominate in the field of oncological hyperthermia. The different electromagnetic heat delivery methods are described hereafter.
2.3.2.1 Radiative hyperthermia

Radiative hyperthermia for heat generation uses the lower frequency waves (RF, MW, far IR and near IR) of the EM spectrum. Among the radiation treatment modalities, RF has the longest wavelength and the largest penetration possibility. To heat large tumors at depth, RF fields in the range of 10–120 MHz are generally used with wavelengths that are long compared to body dimensions and, thus, deposit energy over a sizeable region (Stauffer, 2005). Radiative hyperthermia creates an alternating electric field within the tumor tissue of the patient causing agitation of the ions. This ionic agitation creates frictional heating within the body, which can be tightly controlled through modulation of the amount of RF energy deposited (Habash et al., 2006). Microwave hyperthermia has generally utilized single waveguide microwave antennas working at 434, 915, and 2450 MHz. A widely used method for electromagnetic energy delivery is antenna-array coupling. The body is ringed by the antenna array which delivers a chosen field intensity with controlled phase and frequency. Radiative hyperthermia has an ablative solution also (see review on Thermal ablation). Water-filtered infrared-A hyperthermia is used in regional or whole body hyperthermia (see 2.4.2 and 2.4.3).

2.3.2.2 Magnetic induction hyperthermia

Inductive heating by coupled energy transfer from a coil carrying alternating current (AC) surrounding a biological object through air is used to achieve deeper hyperthermia (for example, more than 5 cm). Magnetic fields in RF induction heating can penetrate tissues, such as subcutaneous fat, without excessive heating. Such magnetic fields induce eddy currents inside the tissues. Since the induced electric fields are parallel to the tissue interface, heating is maximized in muscle rather than in fat. However, the heating pattern is generally toroidal in shape, with a null at the center of the coil. These applicators are usually operated at frequencies of 13.56, 27.12, and 40 MHz, with the depth of penetration typically being a few centimeters (Habash et al., 2006). In order to improve the magnetic energy absorption within the target tissue, magnetic materials, such as microparticles and ferrite rods, may be injected into the targeted area (see paragraph 2.4.4). There is an emerging field of application of magnetic treatments using magnetic suspensions and other magnetic liquids (Laurent et al., 2011).

2.3.3 Ultrasound power deposition

Ultrasound waves involve the propagation of sound waves at frequencies of 2-20 MHz through soft tissues. Unlike EM radiation, ultrasound energy propagates through tissue as travelling pressure waves. Variations in pressure from the alternating compressive and expansive forces cause tissue molecules to vibrate and collide, producing heat from mechanical friction within the molecular structure. Ultrasound delivered hyperthermia may be carried out with external transducers, appropriately coupled to the surface of the body. Ultrasound is significantly more penetrating in fat than in muscle tissue. For example, at 1 MHz the penetration depths are 4.4 cm in muscle and 31.3 cm in fat. The short wavelength in tissue, less than a few millimeters, makes it possible to focus ultrasound energy in small volumes at large depths. Because of the large impedance mismatch between soft tissue and
air and between soft tissue and bone, these interfaces cause almost complete reflection of the ultrasound energy. The anatomic locations where ultrasound can be applied are thus limited. Ultrasound heating has an ablative solution also (see review on Thermal ablation). The primary limitation of such systems is their inability to penetrate air and the difficulty in penetrating bone (Habash et al., 2006).

2.4. Modes of application

Several methods of hyperthermia are currently being used in pre-clinical and clinical practice. These have various subcategories and those are also subdivided further. Traditionally clinical hyperthermia has been divided into three broad categories, namely, (1) localized hyperthermia, (2) regional hyperthermia, and (3) whole-body hyperthermia. In addition, we would like to discuss separately the nanoparticle-mediated hyperthermia as a distinct type of use of hyperthermia, although it forms a local hyperthermia.

2.4.1 Local hyperthermia

In local hyperthermia, heat is applied to a small area restricted to the tumor. Different types of energy may be used to apply heat, including microwave, radiofrequency, and ultrasound. Local hyperthermia is performed with applicators of different kinds (waveguide, spiral, current sheet) placed on the surface of superficial tumors with a contacting medium (bolus). The resulting specific absorption rate (SAR) distribution is subject to strong physical curtailment resulting in a therapeutic depth of only a few centimeters and is even further limited in regions with an irregular surface, such as the head and neck area, or the supraclavicular region (Habash et al., 2006). The penetration depth depends on the frequency and size of the applicator. During local hyperthermia, the tumor temperatures are increased to levels that are as high as possible, as long as the tolerance limits of the surrounding normal tissues are not exceeded (van der Zee, 2002). Candidates for local hyperthermia include chest wall recurrences, superficial malignant melanoma lesions, and lymph node metastases of head and neck tumors. Depending on the tumor location, there are several approaches to local hyperthermia.

2.4.1.1 External local hyperthermia

External local hyperthermia is used to treat tumors that are in or just below the skin. Superficial lesions are the least difficult to heat adequately because of their accessibility and proximity to external energy sources. Heat is usually applied using high-frequency energy waves generated from a source outside the body (such as a radiofrequency or microwave source). External applicators are positioned around or near the appropriate region, and energy is focused on the tumor to raise its temperature. Electromagnetic techniques are generally used for superficial tumors less than approximately 4 cm in depth, such as chest wall recurrence of breast carcinoma, whereas ultrasound beams are useful for somewhat deeper tumors up to approximately 6 cm deep.
2.4.1.2 Intraluminal or endocavitary local hyperthermia

Intraluminal or endocavitary local hyperthermia may be used to treat tumors within or near body cavities. Endocavitary antennas are inserted in natural openings of hollow organs. These include (1) pulmonary (trachea, bronchus); (2) gynecological (cervix, uterus and vagina); (3) genitourinary (prostate, bladder); and (4) gastrointestinal (esophagus, rectum). Very localized heating is possible with this technique by inserting an endotract electrode into lumens of the human body to deliver energy and heat the area directly. This type of thermal therapy is used to achieve temperatures above 45°C to ablate tumors (see review Thermal ablation).

2.4.1.3 Interstitial local hyperthermia

Interstitial local hyperthermia is used to treat tumors deep within the body, such as brain tumors. This technique allows the tumor to be heated to higher temperatures than external techniques. Under anesthesia, probes or needles are inserted into the tumor. Imaging techniques, such as ultrasound, may be used to make sure the probe is properly positioned within the tumor. This type of thermal therapy is used to reach temperatures above 45°C to ablate tumors (see review Thermal ablation).

2.4.2 Regional hyperthermia

Regional hyperthermia attempts to heat moderately large volumes, such as the thorax or pelvis, including the cancerous region as well as surrounding healthy tissue. The remainder of the body is kept as close to normal temperature as possible. Various approaches may be used to heat large areas of tissue. These techniques are intended to heat a large region at depth and usually produce temperatures of approximately 39°C to 42°C throughout the tumor and surrounding region, limited by power deposition in critical normal tissues. Deep tissue approaches may be used to treat cancers within the body, such as cervical or bladder cancer. External applicators are positioned around the body cavity or organ to be treated, and microwave or radiofrequency energy is focused on the area to raise the temperature.

2.4.2.1 Deep regional hyperthermia

External applicators are positioned around the body cavity or organ to be treated, and EM energy is focused on the area to raise its temperature. Deep regional hyperthermia is usually performed using arrays of multiple applicators. An example of a recently developed applicator is called HYPERcollar which comprises a phased-array of 12 RF antennas and focuses heat onto the target while minimizing heating of adjacent critical tissues (Paulides et al., 2007). The HYPERcollar was designed to enable deep heating of the head and neck region, which contains many critical tissues and vessels with a large cooling capacity.

2.4.2.2 Regional perfusion hyperthermia

Regional perfusion hyperthermia is usually applied by perfusion of a limb, organ, or body cavity with heated fluids and is mainly used perioperatively in combination with
Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) is a technique used to treat cancers within the peritoneal cavity (the space within the abdomen that contains the intestines, stomach, and liver), including primary peritoneal mesothelioma (Park et al., 1999) and stomach cancer (Kunisaki et al., 2006; Kerkar et al., 2009). The combination of intraperitoneal chemotherapy used in the operating room with hyperthermia has many different nomenclatures: heated intraoperative intraperitoneal chemotherapy (HIIC), continuous hyperthermic peritoneal perfusion (CHPP), or hyperthermic intraperitoneal chemotherapy (HIPEC). In this review, HIPEC is the designated terminology. The term ‘intraperitoneal’ means that the treatment is delivered to the abdominal cavity. The term ‘hyperthermic chemotherapy’ means that the solution containing chemotherapy is heated to a temperature greater than normal body temperature. During surgery, heated anticancer drugs flow from a warming device through the peritoneal cavity. The peritoneal cavity temperature reaches 41–42°C. Cancer that has spread to the lining surfaces of the peritoneal (abdominal) cavity from primary colorectal cancer, ovarian cancer, gastric cancer, appendiceal cancer or from mesothelioma and pseudomyxoma peritonei, known as peritoneal carcinomatosis, are very difficult to treat. However, when these cancers are confined to the peritoneal cavity, HIPEC becomes an option for candidate patients (Ceelen et al., 2008; Ceelen and Flessner, 2010). There are three main methods of delivery of HIPEC into peritoneal cavity which are described elsewhere (Helm, 2009) and in more detail (Esquivel et al., 2007). Before HIPEC is administered, the surgeon using standard surgical methods will remove all visible tumors that can be removed throughout the peritoneal cavity. This is known as cytoreductive surgery. Following cytoreductive surgery, in the operative setting the surgeon will administer HIPEC treatment. Depending on the type of cytotoxic drug, the duration of chemoperfusion is between 30 and 90 minutes (Ceelen et al., 2008). An increasing number of centers are initiating this multimodality therapy in ovarian cancer and colorectal cancer. Isolated limb infusion (ILI) is a similar technique that has been used to combat cutaneous melanoma of the extremities (Thompson and Kam, 2008). ILI involves drug administration (usually TNF-alfa and/or melphalan) into a limb via percutaneously inserted catheters after vascular isolation of the limb has been achieved with a tourniquet. The infused drug is circulated for a set time via a simple extracorporeal circuit incorporating a heater to produce mild hyperthermia.

2.4.3 Whole-body hyperthermia

Whole-body hyperthermia (WBH) raises the temperature of the entire body up to a fever-range temperature of 39.5°C (i.e. moderate hyperthermia or fever-range hyperthermia) for 4–8 hours or to nearly 42°C for 1–2 hours (Jia and Liu, 2010). The tolerance of liver and brain tissue, however, limits the maximum temperature for using WBH to 41.8–42.0°C, but this temperature may be maintained for several hours. This type of systemic treatment uses homogeneous heating all over the body, with no specific selection of the tumor. WBH produces the most uniform tumor heating, regardless of tumor location within the body. Hence WBH treatment acts differently from local/regional hyperthermia even at the same temperature; in the systemic treatment the blood delivers the heat to the tumor, while in the local/regional treatment the blood at normal body temperature cools the tumor.
Two direct methods are mainly available to carry out systemic hyperthermia; the extra-corporeal and the intra-corporeal treatments. The less frequently used extra-corporeal blood heating transports the blood in a continuous flow through an arterial outlet, pumping the externally heated blood back to the patient. The other method is accomplished by non-invasive means such as the enclosure of a patient in a radiant heat chamber with water-filtered infrared or RF heat input. This non-invasive method rely on heating up the blood in the capillary bed of the corium and sub cutis, which heats up the entire blood stream and in this way the whole body. Water-filtered infrared-A (wIRA) radiation is a type of heat radiation ideally suited to human skin. The application of wIRA distinguishes itself by its high penetration, all the way into the capillary bed of the skin. With wIRA the interfering infrared-B and the infrared-C is eliminated from the heat radiation. Thus a clearly higher radiation power can be applied at a tolerable level than by applying unfiltered heat radiation.

The patient is sedated throughout the WBH procedure, which may last approximately one to four hours. The patient reaches target temperature within approximately 30 minutes, is maintained at 41.8°C, and experiences a one-hour cooling phase. Moderate or fever-range whole body hyperthermia simulates a natural fever increasing the number and activity of natural killer cells, T-helper cells and cytotoxic T-cells. Moderate WBH may also be used to prevent recurrences and is used to treat metastatic cancer that has spread throughout the body. WBH provides a possibility of synergy with conventional therapies. The disadvantages of WBH are the significant systemic stress exerted by whole-body heating, the lack of preferential tumor heating, and the fact that temperatures are limited to approximately 42°C because of thermosensitivity of critical tissues such as the heart, lung, liver, and brain. Thus the thermal goals of systemic therapy are usually more modest than local or regional heating techniques, and intended for activation of drugs or enhancement of immunologic response. For a comprehensive review of the latest devices for WBH see Jia and Liu (2010).

2.4.4 Nanoparticle-mediated hyperthermia

The major problem of applied hyperthermia treatments is achieving a homogenous heat distribution in the treated tissue (Habash et al., 2006). The currently available modalities of hyperthermia are often limited by their inability to selectively target tumor tissue and, hence, they carry a risk of collateral organ damage or they deposit heat in a localized manner, which can result in under-treatment of a tumor. Nanotechnology-based cancer therapy is a special form of interstitial thermotherapy with the advantage of selective heat deposition to the tumor cells. This new therapy is one of the first applications of nanotechnology in medicine and is based on heating of ferric oxide nanoparticles or quantum dots in an external AC magnetic field. The technique consists of the localization of magnetic particles or seeds within tumor tissue followed by exposure to an externally applied magnetic field to cause them to heat (Moroz et al., 2002; Johannsen et al., 2010). The method is also known as magnetic fluid hyperthermia (MFH) or nanohyperthermia. Depending on the duration of treatment and the achieved intratumoral temperatures, the tumor cells are either directly destroyed (see review Thermal ablation) or sensitized for concomitant chemo or radiotherapy. The nanoparticles remain in place at the treatment area, allowing for repeated treatments and the integration of multimodal therapy concepts. Nanoparticle-mediated thermal therapies are being studied worldwide by using either a radiofrequency field, an alternating magnetic field, or near-infrared light as a source of
delivering energy. Different designs of nanoparticle structures (Krishnan et al., 2010; Huang et al., 2011) or thermosensitive liposomes (Ponce et al., 2006; Koning et al., 2010) are in development for energy delivery or as carriers for drug delivery.

2.5 Thermal dose, monitoring and treatment planning

2.5.1 Thermal dose definition

One of the most recognized control parameters for gauging the efficacy of hyperthermia is temperature. Over the years, more than 20 of such parameters have been proposed (de Bruijne et al., 2010). They range from simple temperature statistics (e.g. minimum temperature, median temperature, temperature percentiles, etc.) to thermal isoeffect dose parameters, which convert the time-temperature data into an isoeffect dose (Sapareto and Dewey, 1984; Oleson et al., 1993). The randomized trial by Jones et al. (2005) was the first to prescribe a thermal dose in human patients, using the CEM43°CT90 thermal dose parameter (de Bruijne et al., 2010). CEM43°CT90 represents the thermal isoeffect dose expressed in cumulative equivalent minutes (CEM) at a reference temperature of 43°C based on the low end of the temperature distribution (T90). For a review of the background of the thermal isoeffect dose concept, see Dewhirst et al. (2003).

The dosing and control particularly of deep heat transfer remains a complex issue. The central issue concerning the dosimetric assessment of the absorption of EM energy by biological tissues is how much is absorbed and where it is deposited. This 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. SAR is measured in W/kg. The SAR is determined not only by the incident electromagnetic waves but also by the 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 (Ziskin, 2005). In reality, tumors are far from homogeneous, and their boundaries are not characteristic either. SAR distributions are usually determined from measurements in human models, in animal tissues, or from calculations. SAR values are of key importance when validating possible health hazards and setting safety standards. Various methods are used to obtain point, planar, or whole-body averaged SARs including the use of small electrical field probes or measurement of initial rate of temperature rise in an irradiated object.

2.5.2 Temperature monitoring

Today, a major limitation of hyperthermia is the lack of detailed information available to guide hyperthermia. In order to compare different treatments and to correlate the treatment data with the clinical results, it is mandatory to know what temperatures are reached in the target tissue volume. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumor and surrounding tissue is monitored throughout hyperthermia treatment. However, commonly available technologies do not provide the temperature distribution throughout the tumor. If a tumor is too large for the intended applicator, it is highly unlikely that 100% of the tumor will be adequately heated. The need for sound thermometry measurements is reflected in the various quality assurance
guidelines, i.e. Radiation Therapy Oncology Group (RTOG) and European Society for Hyperthermic Oncology (ESHO) guidelines advise invasive thermometry and provide specific guidelines for temperature registration (Hand et al., 1989; Dewhirst et al., 1990; Lagendijk et al., 1998). Using local anesthesia, small needles or tubes are inserted with tiny thermometers into the treatment area to monitor the temperature. Imaging techniques, such as CT (computed tomography) or ultrasound may be used to make sure the probes are properly positioned. During whole-body hyperthermia treatment, the esophageal, rectal, skin and ambient air temperatures are monitored at 10-minute intervals. Small probes may be inserted into the tumor under a local anesthetic to monitor the temperature of the affected tissue and surrounding tissue. 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 such as infrared thermography, fiberoptic sensors, computed tomography, and magnetic resonance thermal imaging (MRTI) (Craciunescu et al., 2010).

2.5.3 Hyperthermia treatment planning

The time when hyperthermia can be applied must be considered carefully when opted for as an adjuvant therapy. It is conventionally given either before or after another therapy, such as radiotherapy. Most studies have been performed when radiotherapy has been chosen to be given with hyperthermia. It was found that an increased therapeutic ratio could be obtained if radiation was given before heat and an interval of 4 hours or more was allowed (Overgaard, 1980). However, Moros et al. (2010) proposes to administer hyperthermia and radiation simultaneously, rather than sequentially as it is conventionally done, for breast cancer recurrence and others and found that heat induced radio-sensitization increases at thermal doses which can be achieved in the clinic.

Another important issue is to determine which radiation dose-fractionation scheme should be combined with hyperthermia. The optimum radiation dose-fractionation scheme has not been defined yet. In practice, many institutions favor doses of approximately 4 Gy in case of re-irradiation concurrently with hyperthermia for superficial tumors (van der Zee et al., 2010). For deeper-seated lesions, in which there are more sensitive normal tissues, conventional fractionation of 1.8 to 2 Gy has been the rule. Other issues include number of hyperthermia treatments, target temperature and duration, and sequencing of the different modalities. Further phase I and II trials are needed to help define the optimal thermal dose and sequencing of hyperthermia with radiotherapy, including investigation of long-duration, simultaneous radiotherapy plus hyperthermia. The type of treatment planning programs that have already been developed for radiotherapy must be developed for more complex requirements of both prospective and retrospective study of thermal dosimetry in clinical thermal therapy. Since hyperthermia is usually applied in combination with radiotherapy (see 2.6.2), chemotherapy (see 2.6.3), or both (see 2.6.4) the dose and treatment of the other modality will also influence the clinical outcome.
2.6 Mechanisms of synergies - Hyperthermia in combination with other therapies

2.6.1 Hyperthermia alone

The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. Early clinical studies using hyperthermia for the treatment of small, superficial neoplasms have shown that hyperthermia alone, using multiple 30 – 60 minutes hyperthermia sessions, has limited efficacy (e.g. Stewart, 1984). Hyperthermia by itself may result in shrinkage and sometimes complete eradication of tumors, however, these results may not last, and the tumors may come back. Clinical studies evaluating whole-body hyperthermia are primarily in the form of uncontrolled clinical trials. The study populations were generally small and were heterogeneous with respect to disease, site, stage and prior therapy. Today, hyperthermia is almost always used with other forms of cancer therapies as it provides a possibility for synergy with different actions of conventional therapies.

2.6.2 Hyperthermia and radiotherapy

Hyperthermia is considered to be one of the most potent radiosensitizers (Lindner and Issels, 2011). The primary mechanism of radiation therapy is the generation of free oxygen radicals by ionizing radiation, which in turn attacks the DNA of the tumor cells. However cells low in oxygen and pH range or in S-phase, as is often the case for cancers, are relatively radio-resistant (Dewhirst et al., 2005). This is where hyperthermia may be a supplemental aid. Due to the heating of the tissue, blood flow increases, resulting in higher oxygen enrichment in the affected tissue. These effects on blood flow and tumor oxygenation may make the cancer cells more susceptible to radiation therapy. Another important effect is the inhibition of the cancer cells' inherent DNA repair mechanisms as a result of the release of heat-shock proteins by the heat. Hyperthermia increases cytotoxic radiation effects, in particular by interfering with the cellular repair system as a result of the denaturing of the DNA.

The synergistic effects of hyperthermia combined with radiation have been investigated and reported to yield higher complete and durable responses than radiation alone (e.g. van der Zee et al., 2000). Hyperthermia today is probably the most effective support to radiation therapy. It has been reported by many clinical trials (see 3.2) that hyperthermia therapy has been shown to substantially improve local control of cancer, tumor clinical response, and survival rates when added to radiation treatments. It yields considerable therapeutic gain compared to radiation alone in treating various cancerous tumors (Jones et al., 2007). However, clinical experience has largely been limited to treatment of recurrent, metastatic superficial melanomas, chest wall recurrence of breast cancer, cervical cancer and lymph node metastases from head and neck cancers. Tumor depth is a critical factor when combining radiation therapy and hyperthermia. In-vivo studies have shown that the effect of radiotherapy can be increased by hyperthermia by a factor 1.2 to 5 (Horsman and Overgaard, 2007). However, not all studies have shown increased survival in patients receiving the combined treatments (Vasanthan et al., 2005). Systems and techniques have been reviewed to deliver simultaneous thermoradiotherapy of breast cancer (Moros et al., 2010). The synergy between heat and radiation, often expressed as thermal enhancement
ratios, is highest when the two modalities are given simultaneously. When heat precedes radiation, the synergy is lost when the time interval between the two modalities increases. Despite many positive studies and comprehensive reviews, hyperthermia is still not widely accepted as a therapy that can be combined with radiotherapy.

### 2.6.3 Hyperthermia and chemotherapy

The rationale for the combination of cytotoxic drugs with hyperthermia is based on experimental and clinical evidence that heat increases killing of cells by direct thermal toxicity and shows thermal enhancement of drug efficacy (Issels, 2008). 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. When the pore size of cell membranes increase in response to heating, the intracellular drug concentration is also elevated (Ponce et al., 2006). In addition, hyperthermia selectively increases the size of fenestrations, conduits of the drug in tumor vessels, while it does not cause this effect in normal tissues (Ponce et al., 2006). Some other physiology-related features would also make a combination of heat and drugs more attractive. Drugs whose rate-limiting reaction is primarily chemical (i.e., not involving enzymes) would, on thermodynamic grounds, be expected to be more efficient at higher temperatures. The rates of alkylation of DNA, or of conversion of a nonreactive species to a reactive one, can be expected to increase as the temperature increases (Kampinga, 2006). Also, increased DNA damage, decreased DNA repair, and reduced oxygen radical detoxification may have cytotoxic effects as a result of the heat. Concentration of agents that are not normally toxic at normal body temperature can become cytotoxic at 39°C, and in some cases, hyperthermia may overcome some types of drug resistance.

A number of clinical studies indicate that elevated cell tissue temperature, induced by EM energy absorption, significantly enhances the effectiveness of chemotherapy in the treatment of malignant tumors in the human body without increasing the infused amount of drug (e.g. Falk and Issels, 2001). Moderate or even mild hyperthermia (39°C) enhances cell killing in vivo of a number of chemotherapeutic agents, such as mitomycin C, cisplatin, doxorubicin, and bleomycin. Supra-additive cytotoxic effects were observed mainly in combination with alkylants and platinum derivatives. It has been shown that hyperthermia brings about a significantly stronger effect compared to applying chemotherapy only (e.g. Issels, 2006). In combination with chemotherapy, the type of drug, dose, temperature, and time of administration all play a role in determining the effect of treatment. Liposomes have been identified as one of the promising carriers for therapeutic agents to improve drug delivery in the treatment of cancer. Hyperthermia combined with temperature-sensitive liposomes would allow for better control over the release of encapsulated drugs at the disease site.

The microscopic action of chemotherapy, however, is different for local/regional and systemic hyperthermia. The reaction of the given pharmacetics for the local treatment mainly supports a reaction deeper in the tissue while systemic treatment is near the capillaries. Whole body hyperthermia is used in combination with chemotherapy for treatment of advanced cancers especially metastases in different organs, e.g. in the liver,
bones or lungs. The chemotherapy is started at a temperature of about 41°C. Very often it is possible to use lower doses of chemotherapy thus possibly reducing side effects. For patients showing intolerances for specific drugs, for example when they have renal or liver insufficiency or an insufficient blood composition, the same results may be achieved by the combination of decreased chemo-dose and hyperthermia (Wiederman et al., 1993). Tumors or metastases resistant to chemotherapy can also be treated with a combination treatment of chemotherapy and whole body hyperthermia.

2.6.4 Hyperthermia and radiochemotherapy

There is a growing literature on trimodality studies combining hyperthermia with radiotherapy and chemotherapy for head and neck, breast, esophageal, and rectal cancers. Both radio- and chemotherapies mainly act in the vessel neighborhood, because of their higher activity in oxygen-rich tissues and via blood-delivered drug diffusion, respectively. When hyperthermia is applied in combination with radiotherapy and chemotherapy, the dose and treatment scheme of the other modality will also influence the clinical outcome. An extensive review on the combination of hyperthermia with radiochemotherapy was published by Falk and Issels (2001). Thermal radiochemosensitization has more beneficial effects due to the multiple synergies (Bergs et al., 2007).

2.6.5 Integration of hyperthermia with therapies under development

2.6.5.1 Immunotherapy and hyperthermia

Hyperthermia might be effective in the enhancement of anti-tumor immune responses (Overgaard et al., 2009; Franckena et al., 2009). Its use as an adjunct to cancer immunotherapy is supported by an increasing amount of research data. Both pre-clinical and clinical data results have demonstrated improved anti-tumor immune responses with the addition of mild hyperthermia (Tanaka et al., 2005; Issels et al., 2006; Guo et al., 2007; Knippertz et al., 2011; Matsumoto et al., 2011). The molecular mechanisms responsible for the improved immune reactivity observed in the presence of hyperthermia include the generation of heat-shock proteins (HSPs), the activation of antigen presenting cells and changes in lymphocyte trafficking (Appenheimer et al., 2005; Skitzki et al., 2009).

A preclinical study evaluated the use of hyperthermia combined with intra-tumoral injection of dendritic cells (DCs) to treat melanoma (Tanaka et al., 2005). This study aimed to assess the proposed benefits of in situ tumor antigen loading of DCs in the presence of local stimulating factors elicited by hyperthermia. A significant inhibition of tumor growth was noted, with concomitant migration of injected DCs to tumor-draining lymph nodes and priming of cytotoxic T-lymphocytes (CTLs) (Tanaka et al., 2005). Similar findings were obtained in a small clinical study using this treatment strategy (Guo et al., 2007). Patients with advanced melanoma were treated with intra-tumoral injections of immature DCs with or without adjuvant local hyperthermia. The addition of hyperthermia extended the time to tumor progression and improved T-lymphocyte priming (Guo et al., 2007). In a study using a murine prostate cancer model, localized hyperthermia was combined with intra-tumoral injection of DCs (Mukhopadhaya et al., 2007). Tumors treated with a combination of
hyperthermia and intra-tumoral DC injections exhibited significant growth inhibition compared with controls. Matsumoto et al. (2011) explored the feasibility of combining mild hyperthermia and DC application for squamous cell carcinoma (SCC) in vitro and in vivo. A more suppressive effect of tumor growth was observed, and cytotoxic T cell infiltration was significantly increased by adding hyperthermia. Collectively, these findings support the use of hyperthermia activating anti-tumor immune responses.

2.6.5.2 Gene therapy and hyperthermia

The combination of hyperthermia with gene therapy, in which hyperthermia induces transgene expression, represents a promising strategy (Huang et al., 2000; Lohr et al., 2000; Walther and Stein, 2009). In order to treat cancer effectively, the genetic material must exert its effect only on tumor or tumor-associated cells, not on normal cells, and must not eliminate the body’s immune response that is critical in fighting cancer. Different promoters have been used for construction of viral and non-viral vectors and were tested in numerous gene therapy studies for heat-inducible gene expression (Huang et al., 2000; Gerner et al., 2000; Ohtsuru et al., 2001). Successful combination of hyperthermia and HSP-promoter-mediated gene therapy in advanced breast cancer patients has been reported (Ohtsuru et al., 2001). Hyperthermia also improved the results of the HSP-promoter gene therapy by inducing local HSP production and by enhancing the local rate of release from liposome (Gaber et al., 1996). It was shown that this combination therapy was highly selective for mammary carcinoma cells. These studies demonstrated that hyperthermia can efficiently induce transgene expression in vitro and in vivo. Furthermore, these studies showed anti-tumoral efficacy of the combined action of hyperthermia and heat-responsive gene therapy. Next to hyperthermia’s role in increasing and speeding transgene production directly at the site, where needed to enhance therapeutic efficacy, hyperthermia would be expected to help in opening up the pores of tumor blood vessels so that more liposomes reach the tumors and deliver their DNA content to tumor cells. Siddiqui et al. (2009) studied the role of hyperthermia in vitro and in vivo in an attempt to achieve higher transfection rates of viral vectors. However, improvements in intra-tumoral adenoviral spread in response to hyperthermia were not consistently observed in a mouse tumor model using two quantitative endpoints of gene expression. Despite the fact that hyperthermia has long entered clinical practice as therapeutic modality and heat-responsive vectors have been largely improved, showing their effectiveness in vitro and in vivo, currently no clinical trial for heat-responsive gene therapy is underway.

3. Does it work?

3.1 Introduction

Many research studies are being conducted to evaluate the efficacy improvements of hyperthermia. Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy or other modalities. These studies have focused on the treatment of many types of cancer. Many of these studies have shown a significant reduction in tumor size when hyperthermia is combined with other treatments. Table 1 reviews examples of recent outcomes of hyperthermia combination therapy for different
types of cancer. The purpose of this section is to summarize and evaluate the clinical efficacy of hyperthermia combined with other therapies for each anatomical tumor location. Evidence for its efficacy comes from published research studies and clinical trials. The main focus is on phase II and III randomized controlled clinical trials. The clinical value of hyperthermia in addition to other treatment modalities has been shown in many randomized trials. Over one hundred clinical trials are registered in the ClinicalTrials.gov (access September 2011, conditions: cancer; interventions: hyperthermia). The clinical objective is to achieve tumor regression in a controlled fashion. Significant improvement in clinical outcome has been demonstrated for tumors of the bladder, breast, cervix, esophagus, head and neck, melanoma, rectum, and for soft tissue sarcoma. The diversity of the clinical trials can be observed from the diversity of the applied methods. A direct comparison of divergent technical solutions (for example whole-body treatment with RF-ablation in the liver) is not possible. At present, several other studies of the use of hyperthermia in recurrent rectal cancer, anal cancer, peritoneal metastases of ovarian cancer, pancreatic cancer and prostate cancer are under development and/or close to being started (van der Zee and Overgaard, 2009).

An electronic search of the Medline, Embase, Cochrane Library, CancerLit, and ClinicalTrials.gov databases was undertaken in August 2011. In vitro and animal studies, as well as case reports and abstracts have been omitted including studies published before 2005, however, review studies generally go further back in time. Treatments of patients and technologies have evolved over the years and now often consist of different adjuvant chemotherapy and/or radiotherapy implementations. Case reports have been omitted mainly because they are based on an individual patient’s profile hence results cannot be generalized, nevertheless RCT acknowledges their scientific value, however limited. Thus these selection criteria would benefit the rationale for rating the efficacy of hyperthermia based on what is available in clinical practice today.

3.2. Evidence-based results for using hyperthermia per anatomical location

3.2.1 Bladder cancer

Due to the suboptimal clinical outcomes of current therapies for non-muscle-invasive bladder cancer (NMIBC), the search for better therapeutic options continues. One of the developing treatments for high-risk NMIBC is the combination of intra-vesical chemotherapy and hyperthermia, called chemohyperthermia. During the last 15 years, the combined regimen has been tested in different clinical settings.

A systemic review has been performed to evaluate the efficacy of chemohyperthermia as a treatment for NMIBC (Lammers et al., 2011). The primary end point was time to recurrence. Secondary end points included time to progression, bladder preservation rate, and adverse event rate. A total of 22 studies met inclusion criteria and underwent data extraction. Based on three clinical studies with control groups, of which one was a randomized trial, recurrence was seen 59% less after chemohyperthermia than after taking mitomycin C alone. Due to short follow-up, no conclusions could be drawn about time to recurrence and progression. The overall bladder preservation rate after chemohyperthermia was 87.6%. This
rate appeared higher than after mitomycin C alone, but valid comparative studies were lacking. The adverse effects were higher with chemohyperthermia than with mitomycin C alone, but this difference was not statistically significant. The authors of the systemic review concluded that published data suggest a 59% relative reduction in NMIBC recurrence when chemohyperthermia is compared with mitomycin C alone. Chemohyperthermia also appears to improve bladder preservation rate. However, due to a limited number of randomized trials and to heterogeneity in study design, definitive conclusions could not be drawn. The authors further notify that chemohyperthermia may become a standard therapy for high-risk patients with recurrent tumors, for patients who are unsuitable for radical cystectomy, and in cases for which Bacillus Calmette-Guérin treatment is contraindicated.

Colombo et al. (2011) presents long-term efficacy data of intravesical thermochemotherapy vs. chemotherapy alone with mitomycin-C (MMC) randomly administered to 83 patients with intermediate-/high-risk NMIBC as an adjuvant treatment after complete trans-urethral resection. The 10-year disease-free survival rate for thermochemotherapy and chemotherapy alone were 53% and 15%, respectively. Bladder preservation rates for thermochemotherapy and chemotherapy alone were 86% and 79%, respectively. The high rate (53%) of patients who were tumor-free 10 years after treatment completion, as well as the high rate (86%) of bladder preservation, confirms the efficacy of this adjuvant approach for NMIBC at long-term follow-up, even in patients with multiple tumors.

The aim of another study by Halachmi et al. (2011) was to evaluate retrospectively the clinical data of patients with T1G3 NMIBC who underwent complete transurethral resection (TURT) followed by hyperthermia and chemotherapy (mitomycin C) treatment. A total of 51 T1G3 patients were available for analysis. Median follow-up time of tumor-free patients was 18 months (range 2-49 months). Seventeen patients (33.3%) had tumor recurrence and 4 of them progressed to muscle invasive disease. The median time to recurrence was 9 months (range 2-31 months). Here as well the authors concluded that chemohyperthermia can be an effective adjuvant treatment option after TURT to prevent recurrence in patients with T1G3 NMIBC. The progression rate after this treatment was low (7.9%).

3.2.2 Breast Cancer and chest wall recurrences

Patients who suffer superficial recurrences of breast cancer, be it in their chest wall following mastectomy, or in their breast after breast conservation, typically have poor clinical outcomes (Zagar et al., 2010a). There is no accepted standard of care in treating superficial recurrences of breast cancer. The goal of utilizing hyperthermia in breast cancer and chest wall recurrences is to increase response rates in order to prolong disease-free and overall survival. Most reported studies are single institution series or anecdotal case reports. The overall body of evidence suggests that local external superficial hyperthermia, when used as part of a multi-modal regimen, may aid in increasing local tumor response and greater duration of local control. Patients with persistent and/or recurrent breast cancer and chest wall tumors have significantly benefited when hyperthermia has been added to their radio- and/or chemotherapy regimens (Jones et al., 2005; 2007; van der Zee et al., 2010; Wahl et al., 2008; Welz et al., 2005). However, this does not consistently translate into increased survival rates (Jones et al., 2005; Wahl et al., 2008). In 2007 McCormick wrote that
Despite significant research efforts in multiple studies over the past 25 years, convincing results for adopting this therapy as standard care are still lacking.

The 2011 National Comprehensive Cancer Network (NCCN) Breast Cancer Clinical Practice Guidelines in Oncology include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis. There is indeed a substantial literature regarding the combined use of hyperthermia and radiotherapy for the superficial recurrences of breast cancer. Most of it is retrospective in nature, but there are several larger phase III randomized trials that show an improved rate of clinical complete response in patients treated with both modalities (Zagar et al., 2010b). While there is heterogeneity among the study results, a series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone (Jones et al., 2005). No differences in overall survival have been demonstrated. A recent multi-institutional review of repeat irradiation of chest wall and breast for recurrent breast cancer revealed that repeat radiotherapy is feasible for such patients (Wahl et al., 2008).

A more recent review of Zagar et al. (2010b) concludes that in a select group of patients, the addition of hyperthermia to radiotherapy increases the eradication of local tumor, with a modest increase in largely self-limited toxicity. With rigorous thermal dosimetry and careful treatment technique, the addition of heat to radiotherapy can result in long-term local control of breast cancer chest wall recurrences (Zagar et al., 2010b). The most recently reported phase III trial of radiotherapy with or without hyperthermia was performed by Jones et al. (2005). Of the 122 patients enrolled, 108 patients were deemed heatable and were randomized. Of those patients, 65% had disease in their breast or chest wall. Overall, the complete response (CR) rate was 66.1% for patients treated with both heat and radiotherapy, versus 42.3% in the arm which received radiotherapy only. A higher frequency of thermal burns was recorded related to hyperthermia. Van der Zee et al. (2010) performed a large study on re-irradiation combined with hyperthermia in superficial (depth limited to 40 mm from the skin surface) breast cancer recurrences using a custom built multi-applicator multi-amplifier system. They concluded that it is feasible to achieve CR rates of 65% to 90% (depending on size of tumor) in breast cancer recurrences when re-irradiation is combined with hyperthermia. In another study conducted by Oldenborg et al. (2010) on 78 patients with loco-regional recurrent breast cancer in previously radiated areas, it was observed that re-irradiation plus hyperthermia following minimization of tumor burden lead to a high rate of local control compared to historical series, albeit with significant toxicity. Simultaneous superficial thermoradiotherapy of breast cancer has proven to be feasible and safe (Moros et al., 2010).

The addition of hyperthermia to radiotherapy and chemotherapy in cases of chest wall recurrence has been reported previously in only a few studies. The addition of hyperthermia to preoperative radiochemotherapy has been shown to increase CR rates more so than chemotherapy alone (Zagar et al., 2010). However, they conclude that randomized trials need to be performed that look at hyperthermia and chemotherapy versus hyperthermia and chemoradiotherapy or chemoradiotherapy alone, in the neoadjuvant setting to see if hyperthermia adds an advantage. A number of drugs such as liposomal doxorubicin and
paclitaxel have been applied in combination with hyperthermia in a phase I/II study demonstrating their feasibility and tolerance (Vujaskovic et al., 2010).

### 3.2.3 Esophageal cancer

The prognosis of esophageal cancer remains dismal, with a 2-year overall survival after surgery alone of 33-44% (Hulshof et al., 2009). A phase I study investigated the feasibility of external deep loco-regional hyperthermia in localized primarily operable carcinoma of the thoracic esophagus and gastro-esophageal junction in 31 patients (Albregts et al., 2004). Toxicity when combining neo-adjuvant hyperthermia with concurrent chemotherapy (CDDP and etoposide) was evaluated. Since it was concluded from this phase I study that hyperthermia was feasible in esophageal cancer, a phase II study was started combining loco-regional hyperthermia with a chemotherapy (paclitaxel and carboplatin) plus moderate-dose radiotherapy in a neo-adjuvant setting (Hulshof et al., 2009). All patients who completed the planned neo-adjuvant treatment had a R0 esophageal resection. The survival rates at one, two and three years were 79%, 57% and 54% respectively. The authors conclude that preoperative chemoradiation combined with regional hyperthermia resulted in excellent loco-regional tumor control and good overall survival. However, they also admit that it cannot be concluded from this study whether hyperthermia or the new chemoradiation schedule accounts for the outcome.

Treatment options for patients with primary malignant melanoma of the esophagus (PMME) are very limited. For medically or technically inoperable patients, there are no curative options. The first results on patients with PMME have been described in a case report (Hulshof et al., 2010). Two patients with a large obstructive primary malignant melanoma of the esophagus were treated with a combination of external radiotherapy and hyperthermia. Both patients developed a complete local tumor regression, both clinically and endoscopically, without signs of local progression or late toxicity until the end of follow up.

### 3.2.4 Gynecological cancers

Franckena and van der Zee (2010) have reviewed the available literature on the use of various modalities of hyperthermia combined with radiation for various types of gynecological cancers. Hyperthermia for gynecologic cancers can be applied systematically (whole-body hyperthermia), invasively (intraperitoneal, interstitial or intracavitary) or locoregionally. Radiation and hyperthermia has been researched for two main indications in gynecologic oncology: cervix and vaginal cancer. The most widely used form of hyperthermia for gynecological malignancies is loco-regional hyperthermia.

#### 3.2.4.1 Cervical cancer

In a Cochrane review, Lutgens et al. (2010) assessed whether adding hyperthermia to standard radiotherapy for locally advanced cervix carcinoma (LACC) has an impact on (1) local tumor control; (2) survival; and (3) treatment related morbidity. The randomized controlled trials (RCTs) compared radiotherapy alone versus combined hyperthermia and radiotherapy in patients with LACC. Between 1987 and 2009 the results of six RCTs were
published, and used for the review (Chen et al., 1997; Datta et al., 1987; Harima et al., 2001; Sharma et al., 1991; van der Zee, et al., 2000; Vasanthan et al., 2005). Various modalities were used to deliver the energy for hyperthermia treatment. A major drawback of the Cochrane review is that the sequencing of radiotherapy and hyperthermia and the interval between radiotherapy and hyperthermia differed between and within the selected studies analyzed. The results of the analysis with respect to the endpoints studied, i.e. complete response rate following treatment, local recurrence, overall survival and treatment related toxicity grade 3 to 4, indicated a significant improvement of local (pelvic) tumor control and overall survival for the combined treatment modality whereas acute and late toxicity was not significantly different between both treatment groups. Complete tumor response at the end of treatment in the pooled data analysis including 267 study patients yields a significantly better treatment outcome following the combined treatment modality. Local recurrence as endpoint in the pooled data analysis including 264 study patients yields a significantly reduced local recurrence rate. Overall survival as endpoint in the pooled data analysis including 264 study patients yields a significantly better survival for the combined treatment group. The authors conclude that the limited number of patients available for analysis, methodological flaws and a significant over-representation of patients with FIGO stage IIIB prohibited drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy. However, they also report that the available data do suggest that the addition of hyperthermia improves local tumor control and overall survival in patients with locally advanced cervix carcinoma without affecting treatment related grade 3 to 4 acute or late toxicity.

Technologies and methodologies evolve and thus studies based on more recent data may provide a better overview for assessing efficacy of hyperthermia for advanced cervical cancer. The beneficial effects of loco-regional hyperthermia along with radiation for patients with inoperable cervix cancer are confirmed by a recent update of the largest randomized trial (Franckena et al., 2008) and a large follow-up study (Franckena et al., 2009) in an unselected group of patients. Franckena et al. (2008) evaluated the long-term results of the Dutch Deep Hyperthermia Trial after 12 years of follow-up. The Dutch Deep Hyperthermia Trial showed that combining radiotherapy with hyperthermia improved three-year local control rates of 41–61%, as reported in an earlier study. From 1990–1996, a total of 114 women with loco-regionally advanced cervical carcinoma were randomly assigned to radiotherapy or radiotherapy and hyperthermia. The primary end point was local control. Secondary end points were overall survival and late toxicity. At the 12-year follow-up, local control remained better in the radiotherapy and hyperthermia group (37% versus 56%). Survival was persistently better after 12 years: 20% (radiotherapy) and 37% (radiotherapy + hyperthermia). The difference in the cumulative incidence of grades 3–5 radiation-induced toxicities in both groups of patients was not statistically significant. The authors reported that radiotherapy and hyperthermia should be considered for patients with locally advanced cervical cancer and even more so if they are not suited to receive chemotherapy. This was also the conclusion of a recent review (Franckena and van der Zee, 2010). Interestingly, a significant correlation between hyperthermia dose and clinical response was found in a large group of patients with cervix cancer treated with local/regional hyperthermia along with radiation (Franckena et al., 2009).
A combination that is still under clinical evaluation is hyperthermia concurrently applied with radiation and chemotherapy. In a multi-center phase I/II prospective feasibility study, Westermann et al. (2005) studied the efficacy of the combination of hyperthermia, radiotherapy and cisplatin modalities in previously untreated patients with cervical carcinoma. The endpoint was the number of patients who were able to complete treatment, defined as full-dose radiotherapy, at least four cisplatin courses, and at least four hyperthermia courses. At least four courses of chemotherapy were received by 97% of patients, and at least four courses of hyperthermia treatment were received by 93% of patients. Toxicity was fully comparable to that described for chemoradiotherapy alone. The disease-free survival rate at 2 years (from the day of registration in the study) was 71.6%, and the overall survival rate at 2 years was 78.5%. The authors reported that based on this study, an international, randomized, phase III trial of chemoradiotherapy with or without hyperthermia has been launched.

### 3.2.4.2 Ovarian cancer

Overall outcome for women with epithelial ovarian cancer remain relatively poor, and superior methods of treatment are needed (Helm, 2009; 2010). Even after optimal cytoreduction followed by adjuvant chemotherapy, most patients with stage III disease will experience a recurrence (Ceelen, 2009; Leitao and Chi, 2009). In an attempt to improve the unfavorable clinical outcome of relapsed ovarian cancer, hyperthermia has been applied in experimental settings for advanced stages of the disease with concomitant systematic chemotherapy. A prospective phase I/II study of regional abdominal hyperthermia has been performed, combined with systemic chemotherapy in ovarian cancer relapse patients in order to evaluate outcome, efficacy and tolerance (Fotopoulou et al., 2010). The study indicates that hyperthermia can be safely combined with platinum and non-platinum agents in heavily pre-treated patients with relapsed ovarian cancer.

A review by Helm (2009) discusses the role that hyperthermic intra-peritoneal chemotherapy (HIPEC) could play in improving outcomes for women with epithelial ovarian cancer. As we have seen (see 2.4.2.2), intraperitoneal hyperthermia involves the introduction of heated fluid to the abdomen and is mainly used perioperatively in combination with chemotherapy. The rationale for hyperthermic drug administration is based mainly on thermal enhancement of the cytotoxicity of many cytostatic drugs, including the alkylating agents and the platinum compounds (Issels, 2008). The addition of HIPEC to cytoreductive surgery for recurrent epithelial ovarian cancer has been reported in many non-randomized studies cumulatively, including a large number of cases (Table 7, Ceelen et al., 2009; Table 3, Helm 2009). The studies are heterogeneous and difficult to evaluate and compare among themselves and with series reporting cytoreductive surgery alone for recurrent disease (Helm, 2009). In another study, Helm et al. (2010) proposed that HIPEC is a viable additional treatment option for patients with invasive epithelial ovarian cancer and may extend life in selected groups. Ceelen et al. (2009) reported a phase II multi-modal protocol consisting of extensive cytoreduction followed by HIPEC in patients with recurrent, heavily pre-treated ovarian cancer. The objective of this phase II study was to assess the safety and efficacy of extensive cytoreduction and HIPEC in a cohort of patients. The authors conclude that in selected patients with pre-treated recurrent ovarian cancer,
Cytoreduction combined with HIPEC may provide a meaningful overall survival with accepted morbidity. Optimal results, however, are achieved in patients with a macroscopically complete resection and biologically favorable disease. All studies warrant further study in randomized controlled trials (Ceelen et al., 2009; Fotopoulou et al., 2010, Helm et al., 2010).

3.2.4.3 Vaginal cancer

Aktas et al. (2007) evaluated the supplementary value of adding hyperthermia to radiotherapy in patients with primary vaginal cancer. This is the first report and so far the only one of the application of combined radiotherapy and hyperthermia in the treatment of primary vaginal cancer. The authors evaluated 39 patients with vaginal carcinoma who were treated with radiotherapy. Of the 39 patients, 23 had a FIGO stage II tumor and 8 stage III. The criterion to apply hyperthermia in addition to radiotherapy was a stage III tumor with a diameter of more than 4 cm. The 5-year overall survival rate in the whole group of patients was 63%. For stage II tumors it was 59% and for stage III tumors 56%. The 5-year survival for FIGO stages I and IV were 83% and 50%, respectively. The unexpected lack of difference between 5-year overall survival rates for stage II and III tumors found by them may be related to the addition of hyperthermia to radiotherapy in the majority of patients with stage III tumors. These results are suggestive for a beneficial effect of hyperthermia for large size tumors (Aktas et al., 2007; van der Zee et al., 2008).

3.2.5 Head and neck cancer

Until recently, the application of hyperthermia in the head and neck region was limited to superficial regions, mostly lymph nodes, because of the lack of deep-heating equipment for this region. The development of the HYPERcollar applicator system (see 3.4.2.1) has bridged this gap by providing the technology to enable deep heating of the head and neck region, which contains many critical tissues and vessels with a large cooling capacity (Paulides et al., 2007). The first clinical experiences were presented in a study by Paulides et al. (2010). Three patient cases (thyroid, oropharynx and nasal cavity) were analyzed with a focus on the technology involved. The study demonstrated that the focused heating of tumors in the head and neck region is feasible. The phase III study by Hua et al. (2011), which studied the influence of intra-cavitary hyperthermia, provides clinical data supporting the rationale to continue research into the benefit of hyperthermia in the treatment of tumors in the nasopharynx. In this study, 180 patients with nasopharyngeal cancer were randomized to receive radiation either with or without intra-cavitary hyperthermia. Local external microwave hyperthermia was delivered using a commercially available device. The complete response rate in the two arms (radiotherapy plus hyperthermia versus conventional radiotherapy) was 95.6% and 81.1%, respectively. The results from Hua et al. confirm the benefit from hyperthermia when added to radiation for this deeply located site in the head and neck region (Paulides and Van Rhoon, 2011). Equally important was the observation that no increase in early or late toxicity was induced. Another prospective randomized study performed between 2005-2009 by Huilgol et al. (2010) on the combination of hyperthermia and radiotherapy in the treatment of locally advanced head and neck cancer has shown a survival advantage and better response rate when hyperthermia is added to radiotherapy.
3.2.6 Mesothelioma

Most studies in the current literature on mesothelioma have relatively small patient samples; therefore, the clinical implications of these reports are limited. To our knowledge the largest collaborative effort to demonstrate clinical outcomes of patients with peritoneal mesothelioma who were treated by a combined strategy is from Yan et al. (2009). In a multi-institutional registry study, they evaluated cytoreductive surgery combined with hyperthermic intra-peritoneal chemotherapy (HIPEC, see 2.4.2.2) for diffuse malignant peritoneal mesothelioma (DMPM), which represents one fourth of all mesotheliomas. The study included 405 patients with DMPM. The primary end point was overall survival and the secondary end point was evaluation of prognostic variables for overall survival. The median follow-up period was 33 months (range, 1 to 235 months). 79% of patients had epithelial tumors, 6% of patients had positive lymph nodes. The mean peritoneal cancer index was 20. 46% of patients had complete or near-complete cytoreduction and 92% of patients received HIPEC. 31% of patients had grades 3 to 4 complications. The overall median survival was 53 months (1 to 235 months), and 1-, 3- and 5-year survival rates were 81%, 60% and 47%, respectively. Four prognostic factors were independently associated with improved survival in the multivariate analysis: epithelial subtype, absence of lymph node metastasis, completeness of cytoreduction scores of CC-0 or CC-1, and HIPEC. The data suggest that cytoreductive surgery combined with HIPEC achieved prolonged survival in selected patients with DMPM.

3.2.7 Non-Small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) comprises at least 80% of all lung neoplasm and the long-term prognosis for advanced stages (IIIB/IV) which are present in 75% of new cases is poor (Vertrees et al., 2005). The addition of hyperthermia to radiotherapy or chemotherapy is another effort to combat NSCLC. There are rare reports that demonstrate the advantage of combining hyperthermia with radio- or chemotherapy for the treatment of advanced NSCLC. Mitsumori et al. (2007) conducted a multi-center prospective randomized trial to evaluate whether the combination of regional hyperthermia and radiotherapy improved the rate of local control compared to that obtained by radiotherapy alone. A total of 80 patients with locally advanced NSCLC were randomized to receive either standard radiation therapy alone or radiation therapy combined with hyperthermia. The primary endpoint was the local response rate. The secondary endpoints were local progression-free survival and overall survival. The median follow-up period was 204 days for all patients and 450 days for surviving patients. There were no significant differences between the two arms with regard to local response rate or overall survival rate. However, local progression-free survival was better in the radiation and hyperthermia arm. Toxicity was generally mild and no grade 3 late toxicity was observed in either arm. The authors reported that this study failed to show any substantial benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced NSCLC. The quality of this study, however, is compromised by variations in actual treatment and an excessive amount of missing data.

A phase II randomized trial was designed to evaluate the therapeutic efficacy and feasibility of hyperthermia in combination with chemotherapy for patients with advanced NSCLC (Shen
et al., 2011). Eighty patients with advanced NSCLC were divided into two groups. One group of patients was treated by regional hyperthermia in combination with the regimen of gemcitabine and cisplatin, the other group of patients were treated with chemotherapy alone. The clinical benefit response showed a significant difference however not the response rate. The authors concluded from this study that hyperthermia in combination with chemotherapy is a safe, well tolerated, and effective therapeutic modality for patients with NSCLC and that addition of hyperthermia improved quality of life.

3.2.8 Prostate cancer

No consensus on optimal therapy for advanced prostate cancer exists and even though hormonal therapy and radiotherapy are standards, different groups have included hyperthermia associated with radiotherapy to increase its efficiency (Baronzio et al., 2009). Baronzio et al. compared 5 studies to verify if hyperthermia ameliorates the best classical therapy in use, i.e. radiotherapy plus androgen ablation, for advanced prostate cancer. From this analysis, the authors conclude that no amelioration can be obtained adding hyperthermia. They further notify that the possible mechanism which can explain this failure is androgen resistance induced by hyperthermia as demonstrated by Pajonk et al. (2005). In their opinion patients eligible for hyperthermia treatment in association with radiotherapy are those who have developed androgen resistance and are hormone refractory.

More recent research however proved otherwise. Long term results have been reported from a phase II study that assessed the efficacy of trans-rectal ultrasound hyperthermia plus radiation with or without androgen suppression for the treatment of locally advanced prostate cancer (Hurwitz et al., 2011). The study was designed to assess improvement in the 2-year disease-free survival rate compared with the short-term androgen suppression arm in Radiation Therapy Oncology Group (RTOG) study 92-02. Thirty-seven patients were enrolled in this study. The absolute rate of disease-free survival was the primary study end point. A significant benefit was noted with the addition of hyperthermia in this patient population compared prospectively with the study-designed control group of patients who were treated on the short-term androgen suppression arm of RTOG 92-02, 84% and 64% respectively. The current results provide further support to the hypothesis that hyperthermia may be beneficial for the treatment of locally advanced prostate cancer. The authors conclude that hyperthermia combined with radiation for the treatment of locally advanced prostate cancer appeared to be promising, however, only a phase III study can provide conclusive evidence of efficacy. Several recent pilot studies have evaluated whether hyperthermia using magnetic nanoparticles (magnetic fluid hyperthermia, see 2.4.4) can be used for minimally invasive treatment of prostate cancer (reviewed in Krishnan et al., 2010). These results will be discussed in a review on Thermal ablation.

3.2.9 Rectal and colorectal cancer

3.2.9.1 Rectal cancer

In patients with advanced rectal cancer, loco-regional recurrence remains a major problem and a major cause of mortality as well as a source of metastasis to distant organs. Preoperative chemoradiation therapy followed by a total meso-rectal excision is considered
the standard treatment of choice based on a German randomized control trial (Sauer et al., 2004). Better operating techniques, further improvements in local control and survival have been made possible by the additional use of adjuvant radiotherapy. In line with these preoperative treatment developments, the use of hyperthermia in combination with radiotherapy was researched more than a decade ago.

In a Cochrane Review, De Haas-Kock et al. (2009) conducted a systematic review of the literature to study the additional value of hyperthermia if added to radiotherapy in advanced rectal cancer, with respect to pathological complete responses, overall survival and toxicity in rectal cancer therapy. Criteria for considering studies for this review included the outcome measures studied including: overall survival (OS) at 2, 3, 4 and 5-year; local tumor recurrence at 2 and 3 years; severe acute tissue toxicity and severe late tissue toxicity. Severe toxicity is defined as grade 3-4 toxicity and complete tumor response (CR) at 2 months. CR is defined as disappearance of clinical symptoms or as tumor free margins, i.e. microscopically complete (R0) resections, in operated patients. Only phase II and III randomized controlled clinical trials (RCTs) were included in the analysis. Six RCTs published between 1990 and 2007 were identified (Berdov et al., 1990, 1996; Kakehi et al., 1990; You et al., 1993; Trotter et al., 1996; van der Zee et al., 2000). A total number of 520 patients were treated, 258 with radiotherapy only (RT group) and 262 with radiotherapy and hyperthermia (RHT group). The type of interventions included any regimen of pelvic radiotherapy given concurrently or not with a specific hyperthermia regimen. The studies included hyperthermia treatment that was administered regionally, intracavitary or interstitially. After two years, overall survival was significantly better in the RHT group, but this difference disappeared after a longer period (3, 4 and 5 year OS). The chance to develop a CR was significantly higher in the combined treated patient group. Due to limited data the authors were not able to draw firm conclusions about acute or late toxicity. In this review of the available studies the authors reported that the overall quality of studies published is poor, prohibiting definitive conclusions regarding the beneficial effect of hyperthermia added to standard radiotherapy. However, the review shows that adding hyperthermia to radiation in locally advanced and recurrent rectal cancer, can lead to higher short term local/pelvic control rates and a short term survival benefit. The Cochrane review’s final statement is that further studies are needed to compare chemoradiation versus thermoradiation versus chemoradiation plus hyperthermia in well selected/conducted and quality controlled randomized trials.

Other more recent studies not included in the Cochrane review indicated that neoadjuvant radiochemotherapy combined with hyperthermia has beneficial effects. Milani et al (2008) reported results of a multimodal salvage therapy including radiochemotherapy (fluorouracil) and regional hyperthermia in 24 preirradiated patients with recurrent rectal cancer. The median time interval between prior radiotherapy and the onset of local recurrence was 34 months. The primary endpoint was local progression-free survival, secondary endpoints were overall survival, symptom control, and toxicity. The median local progression-free survival was 15 months with a median follow-up of 27 months. The overall 1-year and 3-year survival rates were 87% and 30%, respectively. The authors concluded that radiochemotherapy combined with hyperthermia is an efficient salvage therapy showing high efficacy with acceptable toxicity and can be recommended as treatment option for this unfavorable group of pre-irradiated patients with local recurrence of rectal cancer. Maluta et
al. (2010) reported from a phase II study that pre-operative chemoradiotherapy combined with regional hyperthermia yields acceptable toxicity as well. A more recent study determined the impact of hyperthermia on preoperative radiochemotherapy for locally advanced rectal cancer (Kang et al., 2011). 235 patients with locally advanced rectal cancer were treated with concurrent preoperative radiochemotherapy with or without hyperthermia. The authors withdraw from taking any conclusions due to the fact that temperature measurements were not taken in all patients with hyperthermia. They state that hyperthermia seemed to increase the response of the primary tumor and lymph nodes to preoperative radiochemotherapy in patients with locally advanced rectal cancer, and patients with downstaging showed better survival rates.

3.2.9.2 Colorectal cancer

In the last decades, multimodality therapy encompassing surgery and HIPEC has been proven to provide a significant benefit in selected patients with peritoneal carcinomatosis (Ceelen et al., 2008). A systematic review of relevant studies was conducted by Yan et al. (2006) on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for patients with peritoneal carcinomatosis from colorectal carcinoma. Two randomized controlled trials, one comparative study, one multi-institutional registry study, and 10 most recent case-series studies were evaluated. The level of evidence was low in 13 of the 14 eligible studies. The median survival varied from 13 to 29 months, and 5-year survival rates ranged from 11% to 19%. Patients who received complete cytoreduction benefited most, with median survival varying from 28 to 60 months and 5-year survival ranging from 22% to 49%. The overall morbidity rate varied from 23% to 44%, and the mortality rate ranged from 0% to 12%. The evidence suggested that cytoreductive surgery combined with perioperative intraperitoneal chemotherapy is associated with an improved survival, as compared with systemic chemotherapy for peritoneal carcinomatosis from colorectal carcinoma.

Verwaal et al. (2008) conducted an 8-year follow-up of a randomized trial comparing systemic chemotherapy alone with cytoreduction followed by hyperthermic intraperitoneal chemotherapy and systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Progression-free and disease-specific survival were analyzed and the long-term results were studied in more detail to evaluate efficacy and toxicity. The median progression-free survival was 7.7 months in the control arm and 12.6 months in the HIPEC arm. The median disease-specific survival was 12.6 months in the control arm and 22.2 months in the HIPEC arm. The 5-year survival was 45% for those patients in whom a R1 resection was achieved. The randomized trial shows that cytoreduction followed by HIPEC does significantly add survival time to patients affected by peritoneal carcinomatosis of colorectal origin. For a selected group, there is a possibility of long-term survival. Elias et al. (2009) performed as well a retrospective comparison of a group of patients who underwent cytoreduction and HIPEC with a matched group who received systemic chemotherapy containing oxaliplatin or irinotecan. A significant survival advantage was found in favor of cytoreduction and HIPEC in patients with peritoneal cancer from colorectal cancer (median overall survival 23.9 months versus 62.7 months).
3.2.10 Skin cancer and skin metastases of various primary tumors

A multicenter randomized trial by the European Society for Hyperthermia Oncology (ESHO) investigated the value of hyperthermia as an adjuvant to radiotherapy in the treatment of malignant melanoma (Overgaard et al., 2009). The study describes the results of a previous ESHO report (ESHO 3-85) (Overgaard et al., 1995) but contains a more detailed analysis of parameters related to the outcome of the previous study and a description of the quality of the hyperthermia treatment. Previous experimental and clinical work by Overgaard formed the basis of the treatment schedule prescribed in ESHO 3-85 (Overgaard, 1981; 1986). A total of 134 metastatic of recurrent malignant melanoma lesions in 70 patients were randomized to receive radiotherapy alone or each fraction followed by hyperthermia. The endpoint was persistent complete response in the treated area. Overall, the study showed that the combined treatment resulted in significantly better complete response and local control rates than radiotherapy alone. The complete response rate was 35% and 65% in the radiotherapy alone and the combined arm, respectively, and local control probability after two years and longer 28% and 46%. Especially tumors <4cm which received combined treatment had a much greater response.

The NCCN Guidelines (Version 1.2012) on melanoma has included hyperthermic isolated limb perfusion or infusion as one of the treatment options for patients with unresectable in-transit metastases (category 2B).

3.2.11 Soft tissue sarcomas

Soft tissue sarcomas (STS) are a heterogeneous group of tumors can affect almost all anatomical sites (Stahl et al., 2009). Adult patients with newly diagnosed primary STS of large size (≥5cm) are at risk for developing local recurrence and distant metastasis despite surgical tumor resection (Lindner and Issels, 2011). Neoadjuvant chemotherapy combined with regional hyperthermia is a multimodality treatment scheme which has been under investigation in prospective clinical trials for several years and shows encouraging results in patients with locally advanced high-risk STS (Stahl et al., 2009; Schlemmer et al., 2010; Issels et al., 2010; Lindner and Issels, 2011).

Schlemmer et al. (2010) reported data from a phase II trial examining the efficacy of multimodality treatment with neoadjuvant chemotherapy, hyperthermia, surgery, radiation and postoperative thermochemotherapy in adult patients with high-risk sarcomas of the extremities that were not completely resectable. 47 patients were prospectively treated with a treatment plan of etoposide, ifosfamide and doxorubicin combined with regional hyperthermia followed by surgery, radiation and adjuvant chemotherapy. The multimodality treatment in this trial revealed that response to neoadjuvant thermochemotherapy predicts long term local-failure-free survival for patients with high-risk extremity sarcomas and led to limb preservation in 79% of patients.

The European Society for Hyperthermic Oncology (ESHO) and European Organization for Research and Treatment of Cancer (EORTC) - Soft Tissue and Bone Sarcoma Group (STBSG) conducted a multicenter, randomized phase III study to assess the efficacy and safety of adjuvant chemotherapy with regional hyperthermia in patients with localized high-risk STS (Issels, et al., 2010). Patients were enrolled with primary or recurrent disease. Patients were
randomly assigned to either chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) combined with regional hyperthermia (n=169) or to EIA alone (n=172). The BSD-2000 hyperthermia system (BSD Medical Corporation, Salt Lake City, UT, USA) was used. All patients received comparable local tumor treatment including surgery and radiotherapy. The primary outcome was local progression-free survival (LPFS), defined as the time from randomization to confirmed local progression, relapse, or death, whichever occurred first and irrespective of any occurrence of distant metastases. Secondary endpoints were disease-free survival (DFS), overall survival (OS), tumor response after induction therapy, treatment toxicity, and long-term complications. DFS was defined as the time from randomization to confirmed local failure, distant metastases, or death due to disease or treatment, whichever occurred first. At 2 years, the primary endpoint of local progression-free survival was achieved in 76% of the hyperthermia group versus 61% of the chemotherapy-alone group. Secondary endpoints were also significantly improved by the addition of hyperthermia. The disease-free survival was nearly doubled with 32 versus 18 months and the response rate was more than doubled in the combined treatment arm. The authors report that whether a similar benefit will be seen in lower risk patients, and whether the safety profile will be the same, and hence the tradeoff between benefit and harm worthwhile, remains to be established. However, the role of etoposide remains questionable and might be omitted in future protocols (Lindner and Issels, 2011).

In a phase II study with 39 children (median age 5.2 years) primarily for extracranial non-testicular germ cell tumors, 12 patients with soft tissue sarcomas and three patients with chondrosarcomas had been enrolled. The thermochemotherapy applied consisted of ifosfamide, etoposide, and cisplatin and regional hyperthermia. In combination with hyperthermia, a response of 73% was reported (Wessalowski et al., 2003).

In another study, reirradiation and hyperthermia for radiation-associated sarcoma (RAS) in the thoracic region was examined (de Jong et al., 2011). RAS is defined as the appearance of a sarcoma inside an area previously irradiated with a dose of 25 to 80 Gy, a latency interval of at least 3 years, and a histology clearly distinct from the initial neoplasm for which the radiotherapy was applied. RAS is a very rare disease with a poor prognosis. Because RAS arises by definition in previously irradiated areas, options for full-dose primary or postoperative reirradiation are limited. 16 patients with RAS were treated with reirradiation and hyperthermia. The response rate for 12 patients was 75%, six patients remained free of local failure until last follow-up (8-68 months). The high response rate and the possibility of durable control suggest that this treatment of reirradiation plus hyperthermia for RAS is promising.

4. Is it safe?

4.1. Does hyperthermia have any complications or side effects?

Hyperthermia is mostly applied within a department of radiation oncology under the authority of a radiation oncologist and a medical physicist. Hyperthermia is usually implemented as part of a multimodal, oncological treatment strategy, i.e., in combination with radiotherapy or chemotherapy. The majority of hyperthermia treatments are applied
using external devices, employing energy transfer to tissues by EM technologies. Evaluation of human exposure risk to EM sources or the corresponding heat is a difficult task because it involves many physical, biological, and chemical variables. Guidelines for human exposure to EM fields are generally called maximum permissible exposure (MPE) values, or reference levels. Guidelines recommending limitations in RF exposure have been continually evolving for over a decade. Many countries have developed guidelines by either adopting or adapting the recommendations of major organizations such as the International Commission on Non-Ionizing Radiation Protection (ICNIRP). It should be mentioned that based on the long history of EM exposure in humans, it is reasonably certain that exposures below MPE values have no credible reported adverse health effects and are medically safe (Habash et al., 2003; Feychting et al., 2005).

Most normal tissues are not damaged during whole-body hyperthermia (WBH) if the temperature remains under 43°C. However, due to regional differences in tissue characteristics, higher temperatures may occur in various spots. This can result in burns, blisters, or pain (Falk and Issels, 2001; Kapp et al., 2000; van der Zee et al., 2000). WBH is often uncomfortable for the patient due to these temperature gradients. The overheated area must be monitored continuously in the process (i.e. to avoid sweat accumulation; sweat can heat up excessively and result in blisters on the skin). The subcutaneous fat absorbs four times the amount of energy as the underlying tissues, which can cause problems of temperature-limiting hot spots and increased incidence of skin burns. However, the safe treatment of using hyperthermia could be shown by documented near-eye cases, when the tumor disappeared by the hyperthermia treatment, while the eye remained unhurt and intact from the treatment (van der Zee et al., 2010).

WBH can be applied only to patients in good health. When combined with drugs, the first step must evidently be to demonstrate its safety (van der Zee, 2002). The toxicities associated with WBH may be significant, therefore, careful patient selection and supportive care are essential. Some people are particularly susceptible to the adverse effects of heat, especially the elderly, who are at increased risk of coronary thrombosis in these circumstances, but also infants and people with certain medical conditions and/or who are taking certain medications (Goldstein et al., 2003). WBH may also cause cardiac and vascular disorders, but these effects are uncommon (van der Zee, 2000; Kapp et al., 2000; Wust et al., 2002). Diarrhea, nausea, and vomiting are commonly observed after WBH (Kapp et al., 2000). A number of studies have documented the adverse effects of hyperthermia on the normal adult testis in human (e.g. Mieusset et al., 1995) with a temporary period of partial or complete infertility (e.g. Jannes et al., 1998).

Further studies are in progress using more extensive thermometry and third-generation heating equipment with significantly improved planning and real-time control of heating patterns. These trials should establish the safety and efficacy of hyperthermia in a larger number of disease sites to expand the clinical utility of hyperthermia in the management of cancer.
4.2 Hyperthermia and metastasis

Local hyperthermia causes changes in the tumor microvasculature including increased perfusion and changes in endothelial gap size (Kong et al., 2000; Reinhold, 1988). Consequently, this may cause tumor cell shedding. The question, however, of whether local hyperthermia increases the risk for metastasis is difficult to answer in clinical trials unless the primary therapy has high probability for local control. The question of enhanced metastases with hyperthermia has rarely been examined carefully in human clinical trials where local or regional hyperthermia has been used, however, because many patients in such series already had metastatic disease or had tumors with high likelihood for development of them anyway. The conclusion that can be drawn regarding this issue is that there is no evidence that local-regional hyperthermia causes an increase in metastases. When whole-body hyperthermia is used, the issue is not resolved.

4.3 Risks involved in combining hyperthermia with other therapies

Hyperthermia is generally applied to tumors in combination with radiotherapy or chemotherapy to improve local control. Toxicity with the addition of hyperthermia and radiotherapy is said to be manageable (Zagar et al., 2010). In the most recently reported clinical phase III trial of radiotherapy with or without hyperthermia for superficial tumors, thermal burns occurred in 45% of patients randomized to hyperthermia plus radiotherapy, versus 5.7% in the radiotherapy alone group (Jones et al., 2005). Nearly half of the burns in the combined modality arm were first degree, with only three patients experiencing third-degree burns (Jones et al., 2005). Another point that needs to be taken into account is that cells may develop a resistance to subsequent heat following previous heat treatment (Franckena et al., 2010; Dings et al., 2011). This condition is known as thermotolerance (Habash et al., 2006). In radiotherapy, a standard treatment regimen consists of a six week course of radiation doses. If one would like to apply hyperthermia with each of these radiation treatments, this thermotolerance would certainly negatively interfere with the effectiveness of the treatment. Haveman et al. (2005) indicated in an overview that there are no clear experimental data pointing out an increase in adverse effects specific to the central nervous system after localized or whole-body hyperthermia as a result of combined treatment with chemotherapy. Whether toxicity from chemotherapy is enhanced when applying hyperthermia may depend on the sequence of the two modalities, and on which tissues are heated. It is known from applying perfusion techniques that tissue swelling, blood clots, bleeding, and other damage to the normal tissues in the perfused area can occur; however, most of these side effects are temporary. The peritoneal damage by HIPEC (see 2.4.2.2) is not caused by the hyperthermia but by the peritoneal perfusion with saline solution containing anticancer drugs (Shido et al., 2000).

4.4 Exclusion criteria for using hyperthermia

In some instances hyperthermia cannot be used on patients. Locoregional deep hyperthermia cannot be used for patients with electronic cardiac pacemakers (van der Zee et al., 2010) since it is not possible to guarantee that the electronics of the pacemaker will not be destroyed, resulting in functional disruptions. In addition, 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. Tumor position, region and power levels of the locoregional deep hyperthermia must then be estimated and tailored accordingly.

5. Concluding remarks

Hyperthermia is an emerging therapy method in oncology. It has been indicated in laboratory and clinical studies as an effective modality of cancer treatments, showing significant improvements in clinical responses for a subset of patients when used in combination with other treatment methods such as radio- and/or chemotherapy. In summary, clinical studies have shown the following therapeutic gains from hyperthermia for certain tumor types: improvement in survival rates; increased remission rates; reduced morbidity; reduction in tumor size; improved palliation and quality of life. Exposing tumors to hyperthermic conditions has been shown to be a powerful adjuvant to radiotherapy as demonstrated by recent clinical trials for chest wall recurrences of breast cancer (Jones et al., 2010; van der Zee et al., 2010); locally advanced cervical cancer (Franckena et al., 2009; Franckena and van der Zee, 2010); advanced head and neck cancer (Paulides et al., 2010; Hua et al., 2011), locally advanced prostate cancer (Hurwitz et al., 2011); and malignant melanoma (Overgaard et al., 2009) when compared with radiotherapy alone. Further, a combination of chemotherapy and hyperthermia has been found to improve outcome for non-muscle-invasive bladder cancer (Lammers et al., 2011); recurrent ovarian cancer (Ceelen et al., 2009; Helm et al., 2010); and soft tissue sarcomas (Issels et al., 2010).

Although the efficacy of hyperthermia has been established for some years when used as an adjunct to radiation and/or chemotherapy, it has yet to enter routine clinical practice. In addition, hyperthermia still faces many challenges in oncology. We do not understand clearly the underlying mechanisms, the possible risks and safety issues, and the limits of its applications. Some trials continue to research hyperthermia in combination with other therapies such as immunotherapy for the treatment of different cancers. Other studies focus on improving hyperthermia techniques. For hyperthermia to become an established treatment modality, much work is needed to better understand and exploit the biology of heat in combination with radiotherapy, chemotherapy or novel therapies; improve the equipment used for performing, monitoring and planning hyperthermic treatments; and further define appropriate thermal dose goals and clinical applications.

This review concludes that hyperthermia combined with radiotherapy and/or chemotherapy may provide useful local supportive or palliative effects. The clinical exploitation of hyperthermia was and is still hampered by various challenges including the high degree of interdependency between physiology and biology, technical and clinical limitations, and standardization. Quality hyperthermia requires the coordinated efforts of physicists, technicians, nurses, and physicians. However, these resources are not available at all facilities. Patients who might benefit from this technology should be referred to facilities that have modern equipment and expertise in this area.
6. References

6.1 Scientific publications


Helm CW. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. Oncologist. 2009;14(7):683-94.


Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. Int J Hyperthermia. 2006 May;22(3):191-196.


6.2 Books

Hyperthermia in Cancer Treatment: A Primer. Baronzio GF, Hager ED (Eds.), 2010
The Official Patient's Sourcebook on Hyperthermia: A Revised and Updated Directory for the Internet Age, ICON Health Publications, 2006
Cancer Management in Man: Chemotherapy, Biological Therapy, Hyperthermia and Supporting Measures (Cancer Growth and Progression), Boris R. Minev (Editor), 2011

6.3 Professional Societies/Organizations

Deutsche Gesellschaft für Onkologie (www.dgo-info.de)
European Society for Hyperthermic Oncology (ESHO) (www.esho.info)
Hyperthermie in Nederland (www.hyperthermie.nl)
Interdisziplinäre Arbeitsgruppe (www.hyperthermie.org)
International Clinical Hyperthermia Society (www.hyperthermia-ichs.org)
National Comprehensive Cancer Network (NCCN) (www.nccn.org)
Society for Thermal Medicine (www.thermaltherapy.org)

7. Table
<table>
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<tr>
<th>Therapy</th>
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<td>review</td>
<td>CR 65% to 90% depending on tumor size vs. 32% RT alone</td>
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<td>-</td>
<td>review</td>
<td>CR 66.1% vs. 42.3% RT alone</td>
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<td>114</td>
<td>-</td>
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<td>local control 56% vs. 37% RT alone, OS 37% vs. 20%</td>
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<td>-</td>
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<td>Issels et al., 2010</td>
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C-HT: chemohyperthermia; CRS: cytoreductive surgery; CT: chemotherapy; DFS: disease-free survival; HIPEC: hyperthermic intraperitoneal chemotherapy; LPFS: local progression-free survival; MMC: mitomycin C; RCT: radiochemotherapy; RT: radiotherapy

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