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Heating technology for malignant tumors: a review

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Abstract

The therapeutic application of heat is very effective in cancer treatment. Both hyperthermia, i.e. heating to 39–45°C to induce sensitization to radiotherapy and chemotherapy, and thermal ablation, where temperatures beyond 50°C destroy tumor cells directly are frequently applied in the clinic. Achievement of an effective treatment requires high quality heating equipment, precise thermal dosimetry, and adequate quality assurance. Several types of devices, antennas and heating or power delivery systems have been proposed and developed in recent decades. These vary considerably in technique, heating depth, ability to focus, and in the size of the heating focus. Clinically used heating techniques involve electromagnetic and ultrasonic heating, hyperthermic perfusion and conductive heating. Depending on clinical objectives and available technology, thermal therapies can be subdivided into three broad categories: local, locoregional, or whole body heating. Clinically used local heating techniques include interstitial hyperthermia and ablation, high intensity focused ultrasound (HIFU), scanned focused ultrasound (SFUS), electroporation, nanoparticle heating, intraluminal heating and superficial heating. Locoregional heating techniques include phased array systems, capacitive systems and isolated perfusion. Whole body techniques focus on prevention of heat loss supplemented with energy deposition in the body, e.g. by infrared

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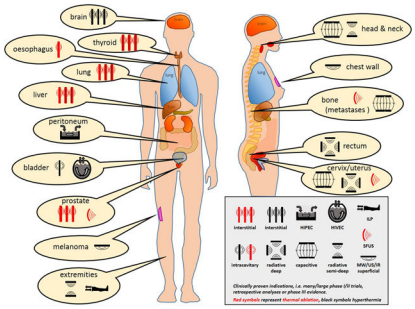
Disclosure statement

R. Ivkov is an inventor on nanoparticle patents. All patents are assigned to either The Johns Hopkins University or Aduro BioTech, Inc. R. Ivkov consults for, and is a member of the Scientific Advisory Board for Imagion Biosystems, a company developing imaging with magnetic iron oxide nanoparticles. R. Ivkov also consults for Magnetic Insight, a company developing magnetic particle imaging. All other authors report no conflicts of interest. The contents of this paper are solely the responsibility of the authors.

radiation. This review presents an overview of clinical hyperthermia and ablation devices used for local, locoregional, and whole body therapy. Proven and experimental clinical applications of thermal ablation and hyperthermia are listed. Methods for temperature measurement and the role of treatment planning to control treatments are discussed briefly, as well as future perspectives for heating technology for the treatment of tumors.

Graphical Abstract:



Schematic overview of clinically proven heating techniques used for various indications and tumor locations.

Keywords

Hyperthermia; thermal therapy; heating equipment; ablation

1. Introduction

Thermal medicine involves the manipulation of body or tissue temperatures for the treatment of diseases. The application of heat has a long history in the treatment of malignant tumors and was already used by the ancient Greeks. In the late 19th century spontaneous regression of malignant tumors was reported in patients suffering from high fevers due to bacterial infections[1]. Since then, heating techniques have been developed to apply more controlled heating to maximize the therapeutic effect while minimizing unwanted side effects. Therapeutic heating of tumor tissue can be roughly categorized as hyperthermia or thermal ablation.

Hyperthermia treatments aim to induce relatively mild tumor heating up to a maximum temperature of 45°C. The therapeutic effect depends on the temperature and the duration of heating (thermal dose)[2–4]. This is often expressed as the cumulative equivalent minutes at 43°C (CEM43)[5, 6], since the widely accepted target temperature is 43°C for up to 1h[6]. The use of CEM43 is based on the Arrhenius relationship, describing the time-temperature dependent cytotoxic effect of hyperthermia[7]. For short exposure times at temperatures below 43°C, the cell survival versus exposure time curve shows a shoulder, which is indicative of accumulation of sub-lethal thermal damage. For increased exposure time, this shoulder turns into a constant rate of cell death, followed after several hours by a lower rate of cell death due to the development of thermotolerance. For heat exposure at temperatures above 43°C, cell death occurs at a constant rate. Although the CEM43 thermal iso-effect

dose concept has some limitations, it is commonly used as a practical normalization to convert a given time–temperature exposure to an equivalent exposure time at 43°C[5]. Hyperthermia is typically applied once or twice a week in combination with radiotherapy and/or chemotherapy schedules and has been shown to enhance the therapeutic effect of these adjuvant treatment modalities. Known mechanisms for this enhancement include inhibition of DNA damage repair, increased blood flow and reoxygenation[8–12]. Furthermore, hyperthermia stimulates the immune response[13]. Optimal dose differs for these mechanisms. Increased blood flow and reoxygenation become active at relatively low temperatures of ~39^{O}C, peak around 41–42^{O}C, and reverse when temperatures exceed 44^{O}C[14]. Effective inhibition of DNA damage repair inhibition requires higher temperatures (exceeding ~41^{O}C) and strongly increases with increasing thermal dose[15]. The combination of all mechanisms above effectively display a dose-effect relationship within the hyperthermia temperature range. The applied timing of delivery is either simultaneous (often for chemotherapy) or sequential with a relatively short time interval between hyperthermia and radiotherapy/chemotherapy.

Thermal ablation aims at generation of temperatures over 50°C for a few minutes in a single session to destroy tumor cells by heat alone. These excessive temperatures cause very rapid cell death by coagulation and protein denaturation, leading to both necrosis and apoptosis, depending on the dose. As explained in the previous paragraph, Arrhenius relationships can also be applied to thermal ablation to predict thermal damage and physical changes associated with thermal exposure in several tissue types[16]. Depending on the mode of energy delivery, thermal ablation can be used as a minimally invasive alternative to surgical resection. However, in the tumor periphery beyond the border of immediate tissue coagulation, non-lethal, but hyperthermic temperatures are achieved and therefore the combination of thermal ablation with chemotherapy, radiotherapy, or immunotherapy, is also attracting growing clinical interest for effectively treating both the tumor and its periphery[17–19]. Figure 1 represents the characteristics of hyperthermia and ablation in terms of temperature levels. Panel B shows a schematic representation of the clear division between the different realms of hyperthermia versus thermal ablation based on data presented in Dewhirst et al[20]. The dividing line shows that the exposure time needed to achieve cell death decreases with increasing temperatures.

Over the past several decades increasing knowledge gained about the mechanisms of action of both hyperthermia and thermal ablation have had positive effects on treatment outcome in several randomized clinical trials for both hyperthermia and thermal ablation[21]. Based on these positive clinical trials, hyperthermia and thermal ablation are recognized in clinical oncology for a number of tumor indications. Hyperthermia is routinely used for locally advanced cervical cancer patients unfit for chemotherapy, for recurrent breast cancer, non-muscle invasive bladder cancer and soft tissue sarcoma. Thermal ablation is currently in routine clinical use for a large number of indications, including hepatocellular carcinoma, renal cell carcinoma (the most common type of kidney cancer), primary and secondary lung tumors, prostate cancer, non-surgical liver metastases and adrenal metastases.

The realization of good clinical results requires high quality heating equipment, and thus a significant amount of research has been undertaken toward the development of robust and

reliable heating devices. The tumor location is often decisive in selecting whether invasive or external heating is preferred. Several types of instruments, antennas and systems have been proposed. These vary widely in physical mechanism of energy transduction, techniques for energy delivery, heating depth and directional control of the delivered energy, as well as in the size of the volume that can be heated[22]. These developments have resulted in dedicated heating equipment for specific tumor sites and anatomical locations, driving significant progress in both the control and technology of heating.

In this review we present an overview of equipment used clinically for hyperthermia and thermal ablation. Different techniques of heating are first explained, followed by an overview of equipment for local, locoregional and whole body heating with a description of tumor sites and clinical applications. Since monitoring is important to ensure treatment quality and thermal dose delivery, control methods involving thermometry and treatment planning are also briefly summarized. Finally, future perspectives are discussed.

2. Methods of heating

Hyperthermia and thermal ablation can be produced using a variety of techniques. Clinically used heating techniques are electromagnetic heating, ultrasound, hyperthermic perfusion and conductive heating. The principles of these techniques are discussed below and a schematic representation of the heating mechanisms is shown in Figure 2.

2.1. Electromagnetic heating

Electromagnetic heating techniques apply a high frequency alternating sinusoidal electromagnetic (EM) field generated using one or more antennas. These EM fields cause dielectric heating by molecular dipole rotation/polarization/vibration in the MHz range and ionic conduction in the kHz range. Polar molecules (e.g. water) have an electric dipole moment and therefore these molecules align continuously with the alternating field. Electric forces cause rotating molecules to push, pull, and collide with other molecules, thereby distributing the energy to adjacent molecules and atoms, causing dielectric heating. In conduction, ions in tissue oscillate due to the forces exerted by the electric current. This current faces internal resistance because of the collisions of charged particles with neighboring molecules or atoms, causing dielectric heating. Tissue heating is dominated by ionic conduction in the extracellular fluid for lower frequencies (< 1 MHz) with the cell membranes acting as isolators, and by dipole polarization at higher frequencies (> 1 MHz). For frequencies > 1 MHz the cell membranes become permeable to the E-fields and the microscopic structure of tissues can be neglected[23].

Electromagnetic heating techniques can be subdivided into categories differing in frequency, wavelength and penetration depth. These include in ascending order of frequency (and descending penetration depth) radiofrequency (either capacitive or radiative), microwave heating, infrared and laser heating. Many microwave systems operate at an industrial, scientific and medical (ISM)-frequency which permits the use outside a Faraday cage for shielding.

2.1.1. Capacitive radiofrequency heating—Capacitive heating is achieved using metal electrodes that are coupled to a high power RF generator, operating at frequencies of 8, 13.56 or 27.12 MHz. Electrodes are usually applied in pairs with the target region positioned between the electrodes, coupled to water bolus bags or other suitable media to transfer the current into the body. These boluses are also applied for skin cooling. An electric field is applied between the electrodes and power is deposited in the tissue as a result of the alternating voltage field[24]. Power can be steered by using different sized electrodes, which concentrate current fields under the smallest electrode, such that both superficial and deep-seated tumor locations can be treated. The energy absorption in tissue by dielectric heating depends on the electrical conductivity and permittivity[25], which vary between different tissue types[26], resulting in an inhomogeneous power distribution. Therefore, excessive temperatures (hot spots) can occur at tissue interfaces, and due to the orientation of the main electric field component, which is perpendicular to fat layers, especially excessive heating of fat tissue can be treatment limiting when using this technique[27–29]. Therefore, capacitive heating becomes less effective with increasing thickness of the fat layer and heating of deep-seated tumors can be challenging[30–32].

Some variants of this heating technique exist, including coplanar electrodes and intraluminal/intracavitary electrodes placed in catheters, which create a capacitor between the electrode and tissue, with electrodes operating as balanced pairs or as individual applicators coupled to an external ground plane.

2.1.2. Radiative radiofrequency and microwave heating—Clinical radiative radiofrequency (RF) hyperthermia is applied using extracorporally placed antennas with operating frequencies ranging from 60 MHz to 150 MHz. RF hyperthermia is used for deep-seated tumor locations (e.g. pelvic tumors) because in this frequency range the wavelength is 25–60 cm in muscle tissue, yielding a large penetration depth of the electromagnetic energy. Microwave hyperthermia is usually applied for superficial or intraluminal/intracavitary tumor sites. Typical free ISM frequencies applied for microwave hyperthermia antennas are 433 MHz (Europe), 915 MHz (USA) and 2450 MHz. To couple the energy into tissue, a water bolus is usually applied between the antenna(s) and the tissue, for both radiofrequency and microwave heating; this water bolus can simultaneously be used for skin cooling when treating deep-seated tumors, or heating in the case of superficial tumor locations. As a result of inhomogeneous energy absorption in different tissues hot spots can occur at tissue interfaces.

Interstitial RF or microwave needles are used for minimally invasive ablation as an alternative to surgery, depending on the size and location of the tumor. Needle electrodes are inserted under image guidance (CT, ultrasound or MRI) into the target tissue. RF ablation applies an alternating current in the range of 350–500 kHz; microwave ablation frequencies are typically 915 MHz or 2.45 GHz. The main difference between RF and microwave ablation is that RF ablation induces areas of high current density mainly near the electrodes, while microwave ablation causes dielectric heating in a volume around the applicator. A rapid decrease of power density away from the applicator is a common trait for both RF and MW ablation techniques[33].

Radiofrequency and microwave hyperthermia and ablation devices can use a single electrode or antenna, an array or a phased array of antennas. With a 2D array of multiple antennas larger tumor areas can be heated. With a 3D phased array, in which multiple antennas are positioned in one or more rings around the patient, power steering and focusing of the electromagnetic energy into the tumor is possible (also at deep-seated locations) by adequate selection of phases and amplitudes to create constructive interference between the electromagnetic fields. As a result of the locoregional heating induced by this technique, some temperature rise in normal tissues is inevitable. However, this is usually not a problem, as long as excessive heating (hot spots) is avoided. This can be realized by adequate (destructive) interference[34].

2.1.3. Infrared and laser—Infrared (IR) heating applies infrared lamps (frequency > 300 GHz) to heat tissues. IR energy is strongly absorbed due to the presence of O-H bonds in water. As the penetration depth of this technique is typically less than 1 cm, it is suitable for very superficial heating. Infrared heating is also applied for whole body hyperthermia, using an isolated cabin to avoid heat loss[35]. Furthermore, optical fiber guided laser light is applied for local ablation of tissue. Interstitial laser ablation allows the delivery of laser energy directly into the tumor tissue, which maximizes penetration and effectiveness in the tumor, while minimizing damage to surrounding healthy tissues[36].

2.2. Ultrasound

Ultrasound (US) heating employs acoustic energy at frequencies 0.5–10 MHz to heat tissues and can be used to induce either hyperthermia or thermal ablation[37, 38]. In contrast to diagnostic US imaging, where fields are usually weakly focused, ultrasound transducers used for thermal therapy are often designed to focus pressure waves to converge on a specific focal zone. Heat is generated by frictional losses due to molecular collisions resulting from the applied US pressure wave. A variety of planar devices (with or without lenses), bowl-shaped sources, focused multi-transducer phased arrays and interstitial US applicators are used. For focused ultrasound (FUS), the ellipsoidal focal spot typically has dimensions of a few mm in diameter, up to ~1 cm in length, which decreases with increasing frequency and aperture. US technology enables excellent spatial and dynamic control of the power and temperature distribution[39] due to its relatively short wavelength (a few millimeters) and allows deep penetration in soft tissues, provided an US window is present. These properties enable conformal tumor heating for both ablation and hyperthermia by mechanically or electronically scanning a highly focused US beam through the target region[40–42].

In addition to thermal effects HIFU also damages cellular structures by cavitation, i.e. implosion of microbubbles formed during HIFU[43–45]. Due to the pressure waves, gas bubbles present in the blood stream start to oscillate in the sound field (stable cavitation) inducing mechanical effects such as the enhancement of the permeability of cell membranes or blood vessels. The latter can be used to open the blood brain barrier locally, allowing drug compounds to extravasate into the brain tissue[46]. Ultrasound-induced cavitation can actively transport and improve the distribution of therapeutic agents in tumors. Injection of microbubbles, polymeric nanocups or other nanoparticles can be used to realize stable and

inertial cavitation, thereby offering a considerable potential for enhanced drug delivery and treatment monitoring in oncological and other biomedical applications[47–50].

Application of US for soft tissue heating requires clear acoustical access to the target tissue, which should not be obstructed by bone, air pockets or strongly absorbing material, such as, for example faeces in the bowels. As the absorption coefficient for ultrasound in bones is about fifty times higher than in soft tissue, any bone in the near field would lead to off-target heating. The acoustic impedance mismatch at the air/tissue interface leads to strong reflection and scattering of ultrasound at air pocket, which may cause local heating and unintentional ablation of adjacent tissue. On the other hand, the strong absorption of US in bone makes it a perfect modality for bone tumor ablation[51, 52], but other lesions may not be accessible for FUS, or require carefully planned applicator positioning to avoid normal tissue hot spots during treatment of deep seated pelvic and abdominal tumor sites.

2.3. Hyperthermic perfusion

Selected anatomical sites are suitable for perfusional hyperthermia techniques, generally combined with chemotherapy. One approach is the direct infusion of heated perfusate into the vascular system, for example for hyperthermic isolated limb perfusion (ILP). ILP involves temporarily connecting the circulatory system in the limb of the patient to an external pump to distribute both heat and drugs to the tumor target region, achieving relatively uniform heating and drug delivery in that region. Another approach is to circulate a hyperthermic carrier solution combined with chemotherapeutic agents inside body cavities to provide heating and drug delivery to tumors in the surface of the cavity. An example is Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) which involves circulation of a heated chemotherapeutic solution in the peritoneal cavity to eradicate any microscopic tumors left behind after surgical removal of macroscopic tumor mass[53]. Hyperthermic intrathoracic chemotherapy (HITHOC) is a similar technique for intrathoracic lesions[54]. Hyperthermic Intra-Vesical Chemotherapy (HIVEC®) is another perfusion technique in which the bladder wall is treated by circulating a heated chemotherapy solution inside the bladder[55].

2.4. Conductive heating

Conductive heating was the earliest clinically applied hyperthermia technique, as it was used by ancient Greeks and Egyptians to treat superficial malignancies. One of the earliest post-industrial revolution hyperthermia techniques was developed by Westermark, using water heated metal coils at 42 – 44°C to treat cervical carcinoma in the late 19th century[56]. More recently, interstitial implants of metal needles with hot water and palladium-nickel thermoseeds have been developed and applied clinically[57]. These conductive heating techniques became less popular because the thermal penetration depth is governed by heat diffusion and perfusion, and therefore small in comparison to other heating techniques.

Magnetic nanoparticles (MNPs) were first proposed by Gilchrist et al in 1957[58]. Further developments have resulted in intriguing materials for clinical conductive heating[59–61]. When exposed to an external magnetic field, the magnetic materials will respond by aligning their atomic moments with the field, thus producing a magnetization that persists for a characteristic duration after the external magnetic field is removed[62, 63]. Heat is generated

via magnetic hysteresis, a loss mechanism for which the amount of energy released depends on the frequency and amplitude of the applied magnetic field, as well as on the intrinsic magnetic properties of the nanoparticle. This dependency is complex and methodology for characterizing the heating is not standardized, making prediction of the amount of heat generated by MNPs challenging[64]. Generally, the relevant frequency range for MNP hysteresis heating is between 0.1 and 1 MHz. However, for clinical MNP hyperthermia a more limited range of about 0.1–0.2 MHz is used to limit excessive off-target tissue heating from induced eddy currents[64]. MNPs are typically suspended in a biocompatible fluid, which enables direct heating of the target tissue, thereby limiting contact with normal tissues[65, 66]. Due to their size (~100 nm) MNPs are colloids, which can be made stable in aqueous suspensions suitable for injection by using appropriate coatings[65–69].

3. Selection and use of equipment based on clinical requirements

Existing heat treatment approaches can be subdivided into three categories as noted earlier: local heating, locoregional heating and whole-body heating. The exposure time to achieve tumor cell death decreases with increasing temperatures (Figure 1). Hyperthermia treatment aims to provide synergistic effects with chemotherapy and/or radiotherapy in a typical 1h treatment, while thermal ablation is applied in a single short session lasting up to a few minutes. A general summary of heating techniques, goal temperatures, treatment scheme and duration is given in Table 1 and in this section an overview of clinical equipment for treatment of local disease (i.e. local and locoregional heating) and treatment of wide-spread disease (i.e. whole-body heating) is presented. At the end of each subsection a brief description of clinical applications is provided. These are summarized per tumor site in Table 2. Figure 3 presents a schematic overview of the heating depth from the skin and the tumor/target size that can be heated with various heating techniques. Figure 4 summarizes the principles of the different heating techniques graphically.

3.1. Local heating techniques

Local heating aims at heating the tumor target volume itself, with no (or minimal) heating of normal tissue surrounding the target. Tumor selective heating can be achieved with invasive applicators for deep seated locations, as used for interstitial heating, electroporation and nanoparticles, or with external applicators for more superficially located target regions. Scanned focused ultrasound with external applicators is the only non-invasive method capable of achieving local and conformal heating at deep seated locations. The different techniques and guiding rationale in each case are discussed in the following subsections.

3.1.1. Interstitial heating

Equipment: Interstitial heating uses arrays of needle shaped applicators implanted into the target volume using catheters. Extensive research has been performed on interstitial heating techniques, resulting in several pre-clinical/research prototypes and commercially available products[70–74]. Investigations include hot sources[75–78], laser sources[79, 80], monopole, dipole, slot or helical coil microwave antennas[81–84], resistively-coupled radiofrequency local current field electrodes[85], capacitively-coupled radiofrequency catheter-based electrodes[86–88] and ultrasound transducers[89]. More detailed reviews of

interstitial heating systems, including detailed system specifications, can be found in the literature[70–74].

Currently, ablative applications are more common, although initially applications of interstitial heating mainly focused on hyperthermia combined with brachytherapy or a brachytherapy boost, where the catheters used to deliver the radiation source can also be used for hyperthermia applicators and thermometry. Energy deposition for all techniques is confined to the close proximity of the individual applicators due to the line/point source nature of interstitial sources. The clinical challenge for interstitial hyperthermia is thus ensuring homogeneous hyperthermic temperatures. This requires close spacing of multiple small applicators within 1–2 cm apart to counterbalance the impact of heat loss due to (high) perfusion. This constrains the application to heating of relatively small tumor volumes[90].

When interstitial radiofrequency electrodes are used, the heating generated by the RF currents between electrodes is strongly influenced by local electrical tissue properties and the location and alignment of the other electrodes[91]. These drawbacks can be overcome by using electrodes operating from within low-loss catheters (e.g. Nylon or Teflon), creating high impedance capacitive coupling across the catheter wall, as in the 27 MHz multiple electrode current source (MECS) system[86–88]. A single probe consists of multiple independent electrodes, each 10–20 mm long. This enables 3D steering of the power deposition. Treatment monitoring and feedback is provided by multi-sensor thermocouple probes, integrated into the electrodes. The power and polarity of the electrodes can be modified to optimize the heating pattern.

Interstitial microwave antennas provide a better penetration depth than radiofrequency electrodes. The most clinically used microwave interstitial hyperthermia system is the commercially available BSD-500 interstitial/superficial system, involving a 915 MHz modified dipole antenna system from BSD – Pyrexar[92]. An 8-channel generator feeds into a 3- or 4-way power splitter to which up to 24 microwave antennas, inserted in standard Celcon or Nylon brachytherapy catheters, can be connected. Depending on the insertion depth, the effectively heated region can be up to ~5 cm in axial length. The antennas can operate in a conservative asynchronous mode or in a synchronous mode. In synchronous mode, the phase of each antenna can be modified with respect to the others to optimize the homogeneity of the power distribution. Up to 8 channels can be used for temperature monitoring using thermistor sensors[92].

The clinical challenge of interstitial ablation is to ensure complete tumor ablation, while avoiding thermal damage to surrounding healthy tissues. Catheter-mounted ultrasound transducers have been explored for interstitial ablation of tissue[93]. The radiating transducer portion can be segmented into separate tubular elements along the catheter length and even into separate sectors around the tube surface. Each sector or segment has individual power control, which provides precise control over both the angular and axial specific absorption rate (SAR) distribution[37, 72, 89]. This concept has been further explored to develop a probe for transurethral treatment of prostate cancer allowing full or focal gland ablation under MR-guidance[94]. The imaging is used for treatment planning as well as for near-real time temperature mapping during therapy with temperature maps being fed back to

the system control for modulating power and device rotation speed[95]. The final CE and FDA approved device, TULSA-PRO was developed and marketed by Profound Medical (Mississauga, Canada). Transrectal US devices, which provide a high degree of spatial control have also been developed[96–98]. However, dwell times between sonications are required to protect the rectal wall from thermal damage, resulting in a relatively long treatment time. The advantage of transurethral US devices is that US is delivered from within the prostate gland, enabling continuous sonication and the use of unfocused beams for reduced treatment times[94].

Radiofrequency ablation (RFA) techniques have matured to facilitate ablation of larger tumors by introducing internal cooling, bipolar, straight and umbrella-shaped clustered probes and combinations of these design elements as strategies to maximize the size of the coagulation zone[99]. However, RFA at high power settings can result in charring of tissue immediately surrounding the electrode. This charring forms an effective insulator, thus limiting the size of the ablated region. Available monopolar RFA devices include the Cool-tip Tyco (Tyco-Valleylab, Boulder, CO, USA) and Radionics (Radionics, Burlington, MA, USA), the multitined RITA StarBurst (RITA Medical Systems, Inc., Mountain View, CA, USA) and RF 3000 Boston LeVeen needles (Boston Scientific Corporate, Natick, MA, USA). Celon Olympus (Medical and Industrial Equipment, Southend-on-Sea, Essex, UK) is a well-known producer of bipolar and multipolar devices. The circumferential HALO^{360+} bipolar RFA system and focal HALO^{90} (Covidien GI Solutions, formerly BÂRRX Medical) were developed for ablating the oesophagus.

Microwave ablation (MWA) is deemed capable of creating larger and more spherical ablation zones than RFA. Applicator cooling and an increase in the number of antennas are used to achieve a larger and a more spherical ablation zone[100]. For ablation of tissues with low electrical conductivity and poor thermal conduction, such as lung tumors, MWA is preferred to RFA. These characteristics do not degrade the volume heating of microwaves, allowing for larger ablation zones than RFA. MWA also allows more energy to be deposited more quickly than with RFA. Although this allows ablation of larger targets, the shape of the coagulation zone becomes less predictable, which increases the risk of adverse effects as intravascular steam burns outside the target. MWA devices operating at 2450 MHz and above are applied to create an ablation zone that is smaller and more spherical than the zone with devices operating at 915 MHz[101–103]. Available devices at 2450 MHz include the cooled 14 gauge mini-choked HS AMICA (HS Hospital Service, Rome, Italy)[104, 105], the Acculis (AngioDynamics, NY, USA)[106], the Solero (AngioDynamics, NY, USA), the Emprint Ablation System (Medtronic Inc, Minneapolis, MN, USA, formerly Covidien)[107, 108] and the NeuWave Certus Microwave Ablation System (NeuWave Medical, Madison, Wisconsin)[109]. For a more detailed overview of 915/2450 MHz devices the reader is referred to Lubner et al[110].

For both in RFA and MWA, the proximity of large blood vessels can cause cool tracks due to their long thermal equilibration length compared to the small lesion size[111]. This convective cooling effect counters the heat generation effects of the ablation devices and requires a modified ablation strategy, such as multi-applicator techniques, to optimize clinical outcome[112].

Besides RF, MW and US applicators, laser techniques are also used for thermal ablation. Laser Interstitial Thermal Therapy (LITT) uses laser light transmitted by an optical fiber which is converted into thermal energy and damages tissue in the target volume. The probe is often cooled to prevent tissue vaporization due to excessively high temperatures near the applicator[113]. An advantage of LITT is that it allows more accurate and safer ablation near critical structures than radiofrequency and microwave ablation. Commercially available systems include the Visualase Thermal Therapy System (Medtronic Inc, Minneapolis, MN) and the NeuroBlate LITT System (Monteris Medical Corporation, Plymouth, MN, USA). The Visualase Thermal Therapy System uses a diffusing fiber optic tip probe (980 nm at 15 W) combined with saline cooling and MRI temperature feedback[114]. Besides diffusing tip probes, the NeuroBlate LITT System provides a gas-cooled side-firing directional diode solid-state laser in the Nd-YAG range (1064 nm at 12 W). Control software-actuated rotational and linear movement is used to achieve spatially-controlled tumor ablation guided by real-time MRI temperature monitoring[80].

Clinical applications of interstitial heating: Clinical use of interstitial hyperthermia includes mainly sites which are also considered suitable for brachytherapy such as prostate cancer, head and neck and brain tumors[71, 90, 115–120]. In a phase II/III randomized trial 79 glioblastoma patients were randomized to receive external beam radiotherapy (59.4Gy; 1.8Gy daily fractions), combined with a brachytherapy boost (60 Gy at 0.40–0.60 Gy/h) +/− 30 min interstitial hyperthermia at 915 MHz immediately before and after brachytherapy. Two year survival was 31% for the hyperthermia group vs. 15% for the brachytherapy alone group[119]. A retrospective analysis of 197 confirmed osteoid osteoma lesions treated with RFA showed this is a safe and effective technique. Two-year follow-up data were available for 126 procedures and showed 89% complete relief of symptoms. The success rate was 91% for initial treatments, and 60% for recurrences ($p<0.001$)[121]. The Surveillance versus Radiofrequency Ablation (SURF) trial randomized 136 patients with Barrett Oesophagus to RFA (n=68) or surveillance (n=68) and found that RFA reduced the risk of progression to high-grade dysplasia or adenocarcinoma to 1.5% for RFA vs 26.5% for control (95% CI, 14.1%−35.9%; $P < 0.001$) and the risk of progression to adenocarcinoma to 1.5% for RFA vs 8.8% for control (95% CI, 0%−14.7%; $P = 0.03$) [122]. A position paper by an international panel of ablation experts established the status of RFA in thermal ablation of colorectal liver metastases and recommended best practice based on 15 papers, each reporting on at least 50 patients, yielding a total of 1613 patients for evaluation. The data thus obtained allowed analysis of various relevant treatment parameters, including size of the tumor lesions that can be treated successfully, which is typically < 3 cm[123].

RFA and MWA are both widely used to ablate thoracic and gastrointenstinal tumors, e.g. liver[110, 124–126], lung[110, 127–129], thyroid[130–133], kidney[134, 135], breast[136], oesophagus[122, 137] and pancreas[138]. MWA is deemed capable of creating larger and more spherical ablation zones than RFA and thus clinical results of MWA are comparable to RFA for smaller lesions, but may be better for larger lesions[124, 125]. A randomized controlled trial involving 76 patients with hepatocellular carcinoma treated with RFA and 76 patients treated with MWA showed that at 2 years 6/98 lesions (6%) had local tumor progression in the MWA arm, versus 12/104 (12%) in the RFA arm ($p=0.27$)[139]. Better

results for MWA versus RFA have also been reported for lung tumors[140]. Vogl et al. found in a retrospective analysis of 109 patients with colorectal lung metastases treated with LITT (21 patients, 31 ablations), RFA (41 patients, 75 ablations), and MWA (47 patients, 125 ablations) that MWA outperformed LITT and RFA in obtaining local tumor control[141]. Narsule et al found both RFA and MWA are a viable option for inoperable patients with early stage non-small cell lung cancer (NSCLC)[142]. MW ablation was also found to be safe, feasible, prevent hemorrhage and capable of eradicating tumors in treatment of hepatic adenomas[143]. A recent meta-analysis concluded that transarterial chemoembolization is more successful when combined with MWA for unresectable hepatocellular carcinoma with tumor size > 5 cm[144].

Clinical use of LITT in brain tumors appears to be safe and to result in better gross total resection combined with less neurologic morbidity than with surgical resection[145, 146]. A multicenter prospective study showed that LITT stabilized the Karnofsky score, preserved quality of life and cognition, and had a steroid-sparing effect in salvage treatment of patients showing progressive brain metastases after stereotactic radiosurgery[147]. LITT is thus currently frequently used as a salvage therapy for treatment of patients with recurrent malignant gliomas[148]. Laser ablation is feasible for bladder cancer as an alternative to transurethral bladder resection, although it remains unclear whether results are comparable due to the lack of randomized trials[149]. Laser ablation also provides a safe and effective treatment of obstructive benign prostatic disease, as demonstrated in a randomized study[150, 151]. Clinical outcome is equivalent to transurethral resection of the prostate (TURP), but with a more favorable toxicity profile; major intraoperative toxicity was absent[150, 151].

3.1.2. Scanned focused ultrasound

Equipment for ablation: US and MR guided scanned HIFU is used for thermal ablation of tumors in a steadily growing number of applications[152]. During treatment, a piezoelectric ultrasound transducer is used to create a highly concentrated focal spot of acoustic energy. This HIFU focal spot is moved through the target region under US or MR guidance, with the aim of inducing temperatures exceeding ~60°C, which result in nearly instantaneous tissue coagulation in the focus while creating minimal thermal damage in the tissue around the focal volume. It is important that sufficient cooling time typically of a few minutes is ensured between sonication at two adjacent locations to prevent prefocal thermal damage. HIFU thus provides a noninvasive form of thermal tumor ablation with a 5–10% lower risk of side effects than for other methods[153]. The heating is localized to the focal volume, and, using long focal length transducers, also more deep-seated locations can be treated. Available CE or FDA approved devices include the Sonablate (SonaCare Medical, Charlotte, NC) and Ablatherm or Focal One® (EDAP TMS, Lyon, France) and the TULSA-PRO (Profound Medical Inc., Mississauga, Canada) for prostate tissue ablation, the Sonalleve system (Profound Medical Inc., Mississauga, Canada) and the ExAblate (InSighTec, Haifa, Israel) for both malignant and benign abdominal tumors and bone metastases. The ExAblate Neuro system uses dedicated phased-array transducers, which eliminates the need for a craniotomy when treating the brain. Up to 1024 ultrasound transducer elements mounted on a ‘helmet’ heat and ablate a deep brain target with no surgical incisions, guided by MR

imaging. FDA approval was received for ablation of brain tissue for treatment of central tremor[154, 155].

Equipment for hyperthermia: In principle MR guided HIFU is also capable of providing a temperature elevation in the mild hyperthermia range over an extended period of time (15–60 minutes), but this application is still experimental. HIFU guided by non-invasive MR thermometry is presently pursued primarily to induce local mild hyperthermia as a trigger for localized tumor-specific drug release from drugs encapsulated in thermosensitive liposomes[156]. Phantom tests with the ExAblate 2100 HIFU ablation system (InSightec Ltd, Haifa, Israel)[157, 158] and preclinical tests with the Sonalleve system (Profound Medical Inc., Mississauga, Canada) have demonstrated the feasibility of inducing a stable MR controlled temperature rise[159–161] resulting in significantly enhanced ThermoDox delivery in mouse[162], rat[163], rabbit[164] and pig models[165]. Using the electronic beam steering of a single HIFU focus limits the size of the maximum volume with a stable elevated temperature level to a few cubic centimeters. Larger volumes -as needed for human treatments- can be heated stably with multi-focus HIFU systems[166], or by a combination of electronic beam steering with a mechanical repositioning of the HIFU transducer[42].

Clinical applications for HIFU: Good clinical results achieved in benign and malignant tumors include ablation of uterine fibroids[167–170], palliation of pain from bone metastases[171] and ablation of prostate tissue[172–177] have resulted in approval of both MR and US guided HIFU for the treatment of these sites in several countries. A prospective multicentre study of 625 patients undergoing HIFU for clinically significant nonmetastatic prostate cancer reported a 5 year failure-free survival, metastasis-free survival, cancer-specific survival, and overall survival of 88%, 98%, 100%, and 99%, respectively, with very few side effects compared to standard whole-gland therapy[173]. A review of 31 uncontrolled studies concluded that HIFU results in short- to medium-term tumor control in treatment of prostate cancer, with a low complication rate comparable with those of established therapies[178]. Successful use of HIFU mediated tumor ablation has been reported in a high number of explorative studies, among others for tumors of the pancreas[138, 179], the breast[180], soft tissue sarcoma[181], pediatric tumors[182, 183], liver[184], kidney[184], oesophagus[185], glioma[186] and other organs[187–189]. A recent pilot study, published in the Lancet Oncology, showed that highly targeted mild hyperthermia (≥39.5°C for at least 30 min) by ultrasound triggered delivery of doxorubicin to liver tumors that were refractory to standard chemotherapy is feasible, safe and able to enhance intratumoral drug delivery, providing targeted chemoablative response[190].

3.1.3. Electroporation

Equipment: Irreversible Electroporation (IRE) is a relatively new interstitial local tumor ablation technique that creates pores in the tumor cell membrane by using a series of very short (e.g. ~100 μs), high voltage direct-current electrical pulses (ranging from hundreds to thousands of V/cm) between electrodes implanted around the tumor[191, 192]. The irreversible aspect is a result of the number of pores created such that a cell cannot recover from the collapse of cell membrane function. Though presented as non-thermal, inclusion of IRE in this review is justified since significant temperature rises in the hyperthermic and in

the thermal ablation range are reported to occur during IRE, significantly contributing to the ablation effect[193–199]. These significant temperature increases are a result of the excessively high SAR generated in a short time (1 – 10 minutes) in the treatment area during IRE, particularly close to the electrodes. Careful placement of the electrodes is essential to manage these effects and prevent damage to surrounding healthy tissue, critical vascular structures and adjacent organs[200].

Clinical applications of IRE: Clinical IRE is performed using the NanoKnife System of Angiodynamics (Latham, NY) and has been applied for treatment of tumors in lung, liver, kidney, pancreas and prostate, and has been proposed as a safer option than conventional ablation for tumors in close proximity to critical structures such as blood vessels and biliary ducts where thermal ablation would have caused serious complications[201–206]. Patients with persistent locally advanced disease after chemotherapy for whom surgical exploration is not feasible could benefit from this less invasive approach[202]. Note that general anesthesia is required with paralytic agents to prevent undesired muscular contractions, as well as careful synchronization with the electrical activity of the heart to avoid arrhythmias that could arise if the administered pulses stray outside of the refractory period of the cardiac cycle. Recently, high-frequency irreversible electroporation (H-FIRE) technology has been developed to enable electroporation of tumors without stimulation of the nearby skeletal muscle; this would avoid the need for general anesthesia[207]. Treatment efficacy decreases with increasing tumor size, and the procedure becomes more challenging with a large number of electrodes. Therefore, IRE should be limited to a maximum tumor diameter of 5 cm[208]. Phase III trials are ongoing, for example comparing chemotherapy plus stereotactic ablative radiotherapy with chemotherapy plus IRE for locally advanced pancreatic cancer.

3.1.4. Ferromagnetic seeds and nanoparticles

Equipment: Ferromagnetic seeds provide a form of conductive interstitial hyperthermia developed for use in conjunction with brachytherapy. The advantage of using ferromagnetic seeds is the absence of a need for connecting wires since the heating is generated by exposing the patient to an external magnetic field, allowing for remotely controlled tissue heating from within the target[209]. Another advantage is the option to use self-regulating alloys, which heat only to the Curie temperature, i.e. the temperature at which a magnetic phase transition from ferromagnetic to paramagnetic occurs. The Curie temperature depends on the alloy composition and can be set to match the desired therapeutic level[210, 211].

Magnetic Fluid Hyperthermia (MFH) uses MNPs for heating the tumor while avoiding toxicity to the surrounding healthy tissue. The quality of the implantation of the nanoparticles in and around the target region, as pre-calculated in a planning system, is important. Nevertheless, by virtue of both variable tumor physical properties and complexities of nanofluid dynamics, nanoparticle distributions in tissue are often inhomogeneous[212], resulting in a heterogeneous temperature distribution. One method to compensate for this is to dynamically adjust the heating by adjusting the magnetic field amplitude[212]. Nanoparticle heat output is non-linear with magnetic field amplitude (i.e. specific loss power $\propto H^2$ *or* H^3). The heat generated by nanoparticles will transfer away from the heat source(s) by conduction and convection, depending on tissue properties and

cooling/heat sink effects of fluid (e.g. blood), respectively. On the other hand, tissue response to heating is also non-linear and dynamic vis a vis thermoregulatory response that changes the heat sink effect, and tissue damage resulting in collapse of perfusion-dependent cooling. Amplitude adjustment exploits these non-linear interactions to explicitly generate intense heat locally for a period of time (high amplitude), followed by a period of reduced heating (low amplitude) to allow time for heat generated to transfer throughout the target tissue. In the ideal scenario, a balance is struck between high/low amplitude cycling that deposits sufficient power to achieve a desired target thermal dose (e.g. CEM43T90 = 60 min). With this technique, the applied power is adjusted based on temperature feedback measured at the tumor-tissue boundary, in combination with a proportional-integral-derivative (PID) control system. Numerical simulations have recently shown that this is a promising strategy to realize a more homogeneous temperature distribution compared with straightforward constant power heating[212].

Clinical applications of ferromagnetic seeds and nanoparticles: Clinical results of ferromagnetic seeds were encouraging; Mack et al. reported minimum and maximum temperatures of 41.0°C and 43.7°C and a 93% total response rate with only 7% grade 3 or 4 toxicity in a study of 44 patients with advanced primary or recurrent extra-cranial solid malignancies[213]. However, optimized performance of ferromagnetic seeds is impaired by the limited 3D temperature control and by the low thermal conductivity of the catheters or coatings, which are needed to implant the seeds or to ensure biocompatibility. This makes it difficult to ensure precision treatment.

Most MNPs are in a preclinical stage of development and clinical experience with MNPs is mainly limited to treating glioblastoma. The brain is a challenging tumor site where other hyperthermia methods are expected to cause major side effects. Results of a single-arm phase 2 study with 59 patients with small (< 4cm) recurrent glioblastoma lesions treated with MNP (median peak tumor temperature 51.2°C) combined with external beam radiotherapy (median biologically effective dose 30 Gy; 5×2 Gy/week) were encouraging with results suggesting a doubling of expected overall survival to 13.2 months, albeit in a favorable patient group[214]. For monitoring tumor progression the use of MRI is excluded due to the very high particle concentrations used, but good alternatives PET and SPECT are available[214]. NanoTherm® AS1 (MagForce Nanotechnologies AG, Berlin), the Iron-Oxide MNP used in this study, was approved for use combined with RT in patients with recurrent glioblastoma in Europe in 2010 and received FDA approval for a trial in prostate cancer patients in the USA.

3.1.5. Intraluminal hyperthermia / HIVEC

Equipment: Intracavitary and intraluminal techniques apply local hyperthermia from within a cavity or lumen, e.g. vagina, oesophagus, urethra or bladder. Heating is generally limited to the lumen and its close proximity up to a depth of ≤1 cm. Both radiative and conductive techniques are available for intraluminal hyperthermia combined with chemotherapy for non-muscle invasive bladder cancer (NMIBC)[215]. Hyperthermic Intra-Vesical Chemotherapy (HIVEC®) involves recirculating a heated chemotherapy solution in the bladder using for example the Combat BRS system (Combat Medical, Wheathampstead,

UK)[55]. Similar commercially available recirculating systems include the Unithermia system (Elmedical Ltd, Hod-Hasharon, Israel)[216] and the BR-TRG-I hyperthermic perfusion system (Guangzhou Bright Medical Technology Co., Ltd. Guangzhou, China) [217]. Recirculation of heated chemotherapy is a technically straightforward form of conductive heating and will give a fairly uniform temperature rise over the bladder wall provided the flow is sufficiently high. Its maximum penetration depth of ~0.5 cm in the bladder wall makes it suitable for early stage NMIBC[218]. Deeper tissue penetration up to ~1 cm is achieved using the Synergo® system (Medical Enterprises, Amsterdam, the Netherlands). This system uses an intracavitary 915MHz microwave antenna in a Foley catheter, which also includes up to five thermocouples to monitor the bladder wall temperature, and two channels for recirculation of the chemotherapy in the bladder[219, 220].

Clinical applications of intraluminal hyperthermia and HIVEC: A recent trial in 161 intermediate and high risk NMIBC patients instilled with pirarubicin demonstrated a 24-month recurrence-free survival of 82.9% in the HIVEC group (n=76, three 45 min 45°C HT sessions 48h apart, 2nd session combined with pirarubicin instillation), versus 63.5% in the non-hyperthermia control group (n=85, p=0.008)[221].

A randomized controlled trial compared thermochemotherapy using the Synergo system (heating to 42±2°C) and chemotherapy alone with Mitomycin C for 83 patients with intermediate-/high-risk NMIBC. Eight weekly 40–60 min treatment sessions were followed by 4-monthly sessions. The 10-year disease-free survival rate was increased from 15% in the Mitomycin C arm to 53% in the Mitomycin C plus hyperthermia arm[222]. Two randomized trials demonstrated that Mitomycin C + Synergo based hyperthermia provides similar or possibly better results compared to standard Bacillus Calmette-Guérin (BCG) treatment for NMIBC patients[223, 224]. Disadvantages of this intracavitary heating approach are an uneven SAR distribution over the bladder wall, and that treatment of more deeply penetrating muscle invasive bladder cancer will require the use of a locoregional hyperthermia device[215, 218].

3.1.6. Superficial hyperthermia

Equipment: In superficial heating, the energy is deposited in a limited volume of tissue close to the heating device. It is therefore applied only to tumors extending up to ~3–4 cm below the skin surface[225]. Several heating devices have been developed for both human[226] and veterinary clinical use[227]. Clinically used superficial heating equipment includes external infrared sources, microwave antennas, radiofrequency electrodes or ultrasound transducers[226].

Superficial tumors infiltrating up to 1.5–2 cm can be treated with infrared heating. The Hydrosun system (Hydrosun medizintechnik GmbH) provides contact free heating of large tumor areas. The penetration depth of infrared is normally less than 1 cm, but the Hydrosun applies water filtering of the radiation emitted by a halogen lamp of high color temperature to ensure effective heating up to 1.5–2 cm depth, and to avoid both overheating of the skin

and tissue dehydration[228]. The Hydrosun system provides real-time infrared thermography measurement and control of superficial temperatures[228].

For superficial lesions with deeper infiltration, microwave heating is often applied. A water bolus with water circulating at a temperature typically around 40°C is used to couple the electromagnetic energy into the tissue. The selected exact water temperature influences the skin temperature and depends on the desired heating depth and whether the skin is target or not[229–231]. Many in-house developed prototypes have been introduced over the years and the first microwave systems usually applied a frequency of 2450 MHz[232, 233]. However, the penetration depth is relatively low at this high frequency, which means that tumors extending to 4 cm beneath the skin will not receive an adequate hyperthermia dose. Significant progress has been made in further development of systems with better penetration depth at 915 and 434 MHz. Furthermore, superficial antennas with various effective field sizes allowing adequate treatment of both small and larger tumor areas have been developed. This has resulted in clear progress in the quality of superficial heating equipment[234–239].

The 915 MHz BSD-500 system (Pyrexar Medical, Salt Lake City, USA), which delivers both interstitial and superficial hyperthermia, provides three different sizes of rigid waveguides: type MA-100, MA-120, and MA-151, with aperture sizes of 10 ×13 cm^2, 18 × 24 cm^2 and 4 × 5 cm^2, respectively. The effective heating areas are somewhat smaller than the aperture size: 8 ×10 cm^2, 12.5 × 19.5 cm^2 and 2.5 × 2.5 cm^2, respectively[225]. A water bolus couples electromagnetic fields into tissue. Additionally, two multi-element applicators are available with this system: an 8-element rigid array (SA-812) and a 24-element flexible array with spiral antennas (SA-24). The SA-812 applicator consists of a closely spaced array of 8 dual-armed Archimedean spiral antennas with a diameter of ~3.5 cm, 7 spirals surround a central spiral[240]. This allows adaptation of the heating pattern to irregularly shaped tumors by using appropriate amplitude settings for the individual antennas. The diameter of the applicator is 14 cm and spiral antennas are deposited on a plexiglass substrate with an integral water bolus. The SA-24 applicator consists of 24 dual-armed Archimedean spiral antennas mounted in a 4×6 array on a rectangular silicone carrier[241]. The applicator is flexible and can follow the body contour. The spiral antennas are connected in pairs of three to one of the eight RF power amplifiers of the BSD-500 system. These spiral antennas are considerably lighter in weight than waveguide applicators, and easier to position near complex patient anatomies. The heating depth of this 915 MHz system is 2–2.5 cm.

Deeper heating, up to 4 cm, can be achieved with 434 MHz antennas. The Yahta-4 system uses contact flexible microstrip applicator (CFMA; SRPC ‘Istok’, Fryazino, Russia) consisting of two coplanar active electrodes and a shield electrode, separated by a thin fluoroplastic substrate[242]. The applicator has an integrated water bolus and can be bent to follow the curvature of the body contour. Five different sizes are available to cover target regions of various dimensions. The smallest antenna, type 1H, has an aperture size of 7.2 × 19.7 cm^2 and the largest, type 3H and 5H, have aperture sizes of 28.7 × 20.7 cm^2 and 19.7 × 28.5 cm^2, respectively, the difference being a 90° shift in field direction. Bending the applicator increases the effective heating depth[243, 244]. The water bolus thickness should not exceed 2 cm in order to avoid resonance effects[245]. The CFMA-SRH applicator has

been developed with characteristics similar to the conventional CFMA, but allows simultaneous application of radiation and hyperthermia[246]. Simultaneous application of radiotherapy and hyperthermia yields comparable thermal enhancement in tumor tissue and normal tissue[247], which could lead to normal tissue toxicity. Therefore, tumor selective heating is important and new types of CFMA-SRH have been developed, consisting of an array of independent microstrip heating elements[238]. Four types of applicators are available, consisting of arrays of 1 × 3, 2 × 2, 3 × 3 and 3 × 4 heating elements. The sizes of the individual heating elements in the arrays range from 6 to 7.5 cm.

The ALBA ON 4000 (ALBA Hyperthermia, Rome, Italy) is a 434 MHz system for superficial hyperthermia, which uses antennas similar to the CFMA, but with a fixed curvature. The system has an integrated thermocouple thermometry system for continuous monitoring of 4–64 temperature sensors. The ALBA Double ON 4000 consists of two treatment units that can be used simultaneously. This allows coverage of larger treatment areas by placing two adjacent applicators, as well as treatment of two separate lesions at the same time.

The lucite cone applicator (LCA) is a 434 MHz water-filled horn applicator developed at Erasmus Medical Center[237]. An advantage of the LCA is the large effective field size, which approaches the aperture size and is ~2.5 times larger than for a conventional waveguide[236]. The aperture size of a single LCA is 10 × 10 cm^2 and multiple antennas can be combined in an array configuration to cover the desired treatment area. In clinical practice, the size and rigidity of the LCA may compromise the treatment set-up and an applicator mounting system is required.

Superficial tumors can extend more than 4 cm deep and heating equipment operating in the microwave range does not provide sufficient penetration depth to heat these tumors effectively. Capacitive heating systems can penetrate to greater depths than 4 cm. Commercially available capacitive systems include the Thermotron RF8 (Yamamoto Vinita Co, Osaka, Japan), EHY-2000+ and EHY-2030 (Oncotherm Kft, Budapest, Hungary), Celsius TCS (Celsius42+ GmbH, Cologne, Germany), HY-DEEP 600WM (Andromedic srl, Velletri, Italy) and Synchrotherm (Synchrotherm, Vigevano, Italy). These systems all operate at a frequency of 8 or 13.56 MHz and because of the large wavelength at these frequencies, temperatures and treated volumes are comparable at 8 and 13.56 MHz. The devices use circular electrodes with an integrated water bolus bag and two opposing electrodes are positioned around the target region. The electrodes used clinically vary between 4 cm and 30 cm in diameter. When using two electrodes of differing size, the energy deposition is concentrated under the smallest electrode. Some systems apply added amplitude modulation in the kHz range to induce either additional non-thermal effects or very localized heating of cell structures. However, the latter has been demonstrated to be physically impossible[248], but research on the nonthermal effects is still ongoing, suggesting that the RF field might affect the mitochondrial function in cancer cells[249, 250] and change cell topography, morphology, motility, adhesion and division[251]. Capacitive variants of the CFMA and CFMA-SRH have also been developed, operating at 27, 40.68 or 70 MHz[238, 242], but clinical use of these antennas is sparse. A clinical limitation of capacitive heating in general

may be excessive heating of fat tissue due to the orientation of the main electric field component[28, 252].

To realize the greater attainable penetration depth with radiative systems, either lower frequencies and/or multi-applicator arrangements are required. Radiative heating systems that provide sufficient penetration to heat deeply infiltrating superficial tumors are the 70 MHz AMC-2 system[253], the 70 MHz breast applicator developed at the Academic Medical Center Amsterdam[254] and the 140 MHz breast applicator developed at Duke University Medical Center[255]. The AMC-2 system has been developed for treatment of deep-seated advanced breast tumors and supraclavicular tumors[253]. The system consists of two horizontally revolving and height adjustable rectangular 70 MHz waveguides. The dorsal antenna is integrated in the treatment table and has an aperture size of 20×34 cm^2. To enhance flexibility of this system. the top waveguide is interchangeable and aperture sizes of 8.5×34 cm^2, 15×34 cm^2 and 20×34 cm^2 can be selected, depending on the treatment location and target dimension. Clinical results demonstrate adequate heating[253]. Both breast applicators have been developed for an intact breast. The 70 MHz AMC breast applicator has a treatment bed fitted with a 50×40×16 cm^3 temperature controlled open water bolus[254]. The patient's breast is immersed in the water and positioned in front of a 70 MHz waveguide in the bottom of the bolus, with aperture size 34×20 cm^2. Clinical results demonstrate adequate heating, though the system is less comfortable for obese patients[254]. The 140 MHz Duke applicator uses a phased-array of four end-loaded dipole antennas, mounted on a Lexan water tank. Geometric focusing is employed, such that each antenna points in the direction of the target[255].

The HYPERcollar is a dedicated phased-array system for more challenging head & neck tumors and has been developed at the Erasmus Medical Center[256]. The system consists of multiple patch antennas, operating at 434 MHz. First clinical results show that the system is safe and feasible[257] and currently an MR-compatible system is under development[258].

Ultrasound energy has also been used to achieve superficial hyperthermia and there has been a similar evolution in technology as for microwave heating. Early devices applied single transducers operating at 0.5–3.5 MHz and only small superficial lesions could be treated[259]. The Sonotherm 1000 system (Labthermics Technologies Inc, Champaign, Il) provides two sizes of multi-sector applicators, combining multiple transducers in a non-focused planar array[260–263]. Each sector can be adapted individually to realize a uniform heating pattern. A 16-sector applicator of 15×15 cm^2 has been developed to heat larger superficial tumor volumes with a depth up to 8 cm. A smaller 4-sector applicator of 7.5 × 7.5 cm^2 allows treatment of anatomical sites difficult to reach with the large applicator, such as the head & neck. The treatment depth can be varied by changing the frequency (1 or 3.4 MHz). The system has a 16 channel thermometry system for thermocouple based thermometry and a therapy control algorithm controls the energy deposition, based on the information of the temperature measurement points.

Clinical applications of superficial heating: Superficial heating is commonly applied to melanoma, head & neck cancer, and chest wall recurrences of breast cancer with good clinical results The importance of sufficient heating depth to achieve good tumor response

was demonstrated for example by Van der Zee et al, who compared 2450 MHz and 434 MHz for treatment of recurrent breast cancer[232]. Re-irradiation (eight fractions of 4 Gy twice weekly) was combined with 60 min hyperthermia. The complete response rate (CR) was 74%, but for tumors with a diameter larger than 3 cm heating at 2450 MHz was less effective (65%) than for smaller tumors (CR 87%). Heating at 434 MHz performed equally well for tumors larger or smaller than 3 cm.

Randomized trials have demonstrated the effectiveness of radiation combined with microwave hyperthermia for recurrent breast cancer[264]. Vernon et al combined the results of five randomized trials for radiation +/− hyperthermia for superficial localized locally advanced and recurrent breast cancer and found an increase in overall CR rate from 41% with radiotherapy alone to 59% for combination with hyperthermia[265]. The greatest effect was observed in patients with recurrent lesions in previously irradiated areas, where the re-irradiation dose was limited. A randomized trial by Jones et al confirmed this good response and also showed that the effect was even better for previously irradiated patients[266]. For this group the CR was 23.5% for re-irradiation alone versus 68.2% in the re-irradiation plus hyperthermia arm. In a recent study very good results were also reported for water-filtered infrared heating using the Hydrosun system combined with hypofractionated re-irradiation (4 Gy once per week up to a total dose of 20 Gy, within 1–4 min after heating) for heavily pre-treated patients with large breast cancer recurrences[228]. A complete response rate of 61% was observed in patients with macroscopic disease with only grade 1 toxicity. This study suggests that even repeated re-irradiation could be considered as a treatment option when combined with hyperthermia.

The value of microwave superficial hyperthermia as an adjuvant to radiotherapy was also demonstrated in a multi-center randomized trial for patients with recurrent or metastatic malignant melanoma[267]. After a combined treatment of radiotherapy (three fractions of 8 or 9 Gy in 8 days) plus 60 min hyperthermia 2-year tumor control was 46%, compared with 28% with radiation alone[268].

Treatment of recurrent breast tumors with infiltration beyond 4 cm is more challenging. Capacitive heating yields sufficient penetration depth and allows therapeutic temperatures to be achieved, but temperature distributions can be very heterogeneous with treatment limiting hot spots [252]. The feasibility of adequate heating of these tumors with fewer hot spots has been demonstrated with the radiative 70 MHz AMC-2 system[253] and with the 70 MHz AMC breast applicator[254].

Capacitive hyperthermia has been demonstrated to be an effective technique for heating locally advanced head & neck tumors. A randomized trial comparing radiotherapy (66–70 Gy in 6.5–7 weeks) with radiotherapy plus weekly hyperthermia for 30 min showed that adding hyperthermia increased the complete response rate from 42.4% to 78.6% [269]. No excessive thermal toxicity was reported in this study.

Clinical results for ultrasound hyperthermia using the Sonotherm 1000 system have been reported for tumors in four sites: groin/trunk, axilla, breast or chest wall, and head & neck[263]. Therapeutic heating levels are feasible and of these categories groin and trunk

tumors were most effectively heated. Head & neck tumors proved more difficult to heat with only 8% of the measurement points exceeding 42°C.

3.2. Locoregional heating techniques

Locoregional hyperthermia aims at heating the tumor target volume plus an additional margin of normal tissue. Locoregional heating techniques include electromagnetic heating, Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) and isolated perfusion. Extending heating to an additional normal tissue margin is effective for pre-heating of blood supply to the tumor or to treat microscopic spread outside the macroscopic tumor.

3.2.1. Electromagnetic locoregional heating

Equipment: Electromagnetic locoregional heating uses external heating devices with antennas positioned around the patient and is typically applied for deep-seated tumors, for example in the pelvic or abdominal region. In contrast to more focused techniques such as HIFU, with locoregional heating the region around the tumor is also heated to some extent and the temperature distribution is largely determined by the individual anatomy. In the pelvis tumor heating is sometimes restricted by hot spots near bony and fatty tissues. Compared with local heating techniques, locoregional heating allows a more homogeneous temperature distribution in the target region to be achieved, since the heated volume is larger, including a large normal tissue margin, and the inflowing blood will be slightly preheated and thus cause less cooling[111]. Mild heating of normal tissue around the tumor will usually not increase normal tissue toxicity when radiotherapy and hyperthermia are applied sequentially with a short time interval[270–272]. However, hot spots in normal tissue should be avoided. These are manifested as complaints of pain when the temperature exceeds 45°C. These hot spots typically occur at tissue interfaces associated with a large contrast in dielectric and thermal tissue properties, e.g. going from muscle to fat or bone, particularly if the E-field is perpendicular to these interfaces. Pace-makers and metallic implants in the treatment region are usually a contra-indication for treatment.

Electromagnetic locoregional heating can be performed using capacitive heating devices or radiative phased-array systems. Commercially available capacitive heating systems have already been discussed in the section *"Superficial Hyperthermia".* For deep heating of centrally located tumors equally sized electrodes with a diameter ≥ 25 cm are usually used. These double-electrode systems have no power steering potential to avoid hot spots. The choice of bolus and its specific design is important for capacitive heating to reduce heating of the superficial fat layers, which is a serious risk because the main E-Field direction is perpendicular to the superficial fat layers. Overlay boluses can be used for more aggressive skin cooling[273], but achievable temperatures at deep-seated tumor locations decrease for increasing fat layer thickness[29].

Radiative phased array systems consist of multiple antennas organized in one or more rings and allow power steering by adapting phase amplitude settings of the individual antennas or antenna pairs. The dominant E-field direction is parallel to the superficial fat layers, i.e. in cranial-caudal direction. Focusing of the electromagnetic energy on the tumor location, as well as suppression of severe hot spots in normal tissue can be realized by adjusting phase

and amplitude settings for power steering to create constructive interference in the tumor and destructive interference at hot spot locations among the electromagnetic fields radiated by the antennas[274–276]. In the applied frequency range, i.e. between 60 and 150 MHz, the heating focus is typically 10–15 cm in diameter, which allows heating of larger tumors compared to other techniques (Figure 3). Commercially available phased-array systems are the BSD-2000 systems (Pyrexar Medical, Salt Lake City, USA) [275, 277] and the ALBA 4D system (ALBA Hyperthermia, Rome, Italy)[278]. Because of the large number of degrees of freedom of these systems, optimization of antenna settings by treatment planning is becoming increasingly common (see section Treatment planning) and has been validated for both systems[279–282].

The BSD-2000 systems include the Sigma-60 system and the smaller bore Sigma-30, with 8 paired dipoles organized in one ring and the Sigma-Eye system, with 24 paired dipoles distributed over three rings, which allows improved power steering properties. Cross-coupling between antennas in the dipole array can affect phase-amplitude control during clinical applications[283, 284], but online adjustments can overcome this problem[285]. A hybrid version of the Sigma-30 and Sigma-Eye system has been integrated in suitable MR-scanners to enable non-invasive MR-thermometry. The first prototype of this MR-HT hybrid system was installed and evaluated at Charité Berlin using a Siemens Symphony 1.5 T scanner[286–288]. Other versions employ a 1.5 T Philips Ingenia MR system and a 1.5 T GE MR450w MR system[289]. More details on the status of MR thermography are given in the thermometry section.

The ALBA-4D system consists of four rectangular waveguides organized in one ring and is similar to the AMC-4 system, developed and built by the Academic Medical Center Amsterdam[290]. The AMC-8 system, with 8 rectangular waveguides in two rings, has also been developed and built by the Academic Medical Center Amsterdam[291]. This system has a greater heating length and improved power steering compared with the single ring AMC-4 system.

Clinical applications of electromagnetic locoregional heating: Capacitive locoregional heating has been investigated for several tumor locations, such as lung[292–297], prostate[298, 299], bladder[300–302], rectum[303, 304] and liver[305, 306], and treatments were generally deemed feasible. Degrees of clinical success are usually varying, but good clinical results can be achieved with capacitive hyperthermia, provided that the patient has only a thin superficial fat layer[29]. Increasing temperatures to 38–39°C have shown a significant increase in tumor blood perfusion for cervical cancer patients[30]. Early results of an ongoing phase III trial using the EHY-2000+ device report improved 6 month local disease control for cervical cancer patients treated with radiochemotherapy combined with capacitive hyperthermia (45.5%) compared to radiochemotherapy alone (24.1%)[307]. A multicenter randomized study in cervical cancer patients showed that cisplatin-based radiochemotherapy plus weekly hyperthermia for 60 min using capacitive heating (Thermotron RF8) resulted in a higher 5-year complete response rate (88%) than with radiochemotherapy alone (77.6%)[308]. Clinical outcome appeared to depend on the thermal dose achieved; a successive analysis showed that a thermal dose of at least one cumulative equivalent minute at 43°C (CEM43T90 ≥1) is required for a significant effect of

hyperthermia[31]. A phase III prospective, randomized controlled trial demonstrated the effectiveness of capacitive hyperthermia in patients with painful bony metastases[309]. Radiotherapy (10×3Gy) plus twice weekly hyperthermia for 40 min showed a significant increase in pain control rate and an extended response duration compared to radiotherapy alone. The accumulated complete response rate within 3 months after treatment was 58.6% in the radiotherapy+hyperthermia group versus 32.1% in the radiotherapy-alone group[309].

Excellent clinical results have been achieved with radiative locoregional heating of deep-seated tumors in the pelvis, including cervix, bladder, rectum, sarcoma and pediatric tumors. The Dutch deep hyperthermia trial showed the beneficial effect of combining standard radiotherapy with 60 min weekly hyperthermia for pelvic tumors (cervix, rectum, bladder) [272]. The treatment effect did not differ significantly with tumor site, but adding hyperthermia seemed to be most effective for cervical cancer, for which 3-year overall survival was 27% in the radiotherapy group and 51% in the radiotherapy plus hyperthermia group[272]. After 12 years the survival of the patients in the radiotherapy plus hyperthermia group was still twice as high as survival in the radiotherapy-arm (37% vs 20%)[310]. A randomized phase III trial for soft-tissue sarcoma demonstrated that adding 60 min hyperthermia to chemotherapy (etoposide, ifosfamide and doxorubicin) on day 1 and 4 for each cycle significantly improves long-term outcome, with a 10-year survival of 52.6% for chemotherapy plus hyperthermia versus 42.7% for chemotherapy alone[311]. The combination of hyperthermia plus chemotherapy is also very important in treatment of pediatric sarcoma or germ cell tumors that respond poorly to chemotherapy, or recur after chemotherapy[312–314]. A prospective study reported a 5-year survival of 72% and the long-term prognosis was almost similar to those for patients receiving first-line chemotherapy treatment[312]. Ongoing clinical trials evaluate the addition of radiative locoregional hyperthermia to chemotherapy in treatment of e.g. pancreatic cancer[315], or to chemoradiation in treatment of e.g. rectum, pancreatic and anal cancer[316–318].

3.2.2. HIPEC

Equipment: Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) is a procedure during which a solution containing chemotherapeutic drugs is maintained at an elevated temperature level (41–43°C) and circulated in the peritoneal cavity (abdomen) for a period of 30–90 minutes, aiming at eradication of microscopic tumor lesions of peritoneal carcinomatosis (PC). As drug penetration is limited to a few millimeters[319]. HIPEC is generally preceded by cytoreductive surgery (CRS), surgical removal of macroscopic tumor[53]. Commercially available HIPEC devices consist of a peristaltic or roller pump, a temperature controlled container for the chemotherapy, tubing to transport chemotherapy to and from the patient and temperature probes to be used in the peritoneal cavity. Systems used include the ThermoChem™ HT-1000 and HT-2000 (ThermaSolutions, White Bear Lake, MN, USA), Performer (RAND Biotech, Medolla, Italy) and other devices. The chemoperfusion technique is either ‘closed’ (with temporary skin closure during chemoperfusion) or ‘open’ (the coliseum technique, referring to the skin being pulled upward around the open peritoneal cavity) during HIPEC[53]. Both approaches have specific advantages in terms of flow and temperature management during HIPEC.

Clinical applications of HIPEC: Clinical application of HIPEC has gained much popularity in the last decade[320–326], with promising results in stage III ovarian cancer and in gastric cancer with peritoneal metastases. A phase III study comparing cytoreductive surgery with surgery plus 90 min HIPEC with cisplatin at 40°C for ovarian cancer reported that HIPEC increased the median overall survival from 33.9 months to 45.7 months after a median follow-up of 4.7 years, with no significant difference in side-effects[327]. In gastric cancer with peritoneal metastases, a recent retrospective multicenter comparison with propensity score based matching of CRS alone versus CRS combined with HIPEC showed that the addition of HIPEC improved overall survival from 12 to 19 months (hazard ratio 0.42 – 0.86; p = 0.005)[328]. In colorectal cancer with peritoneal metastases (PM), the place of HIPEC remains uncertain. A Dutch randomized trial comparing IV chemotherapy alone (only fluorouracil with leucovorin) with CRS and 90 min mitomycin C-based HIPEC at 41–42°C inflow temperature showed that the median survival doubled from 12.6 months with standard therapy to 22.3 months with CRS and HIPEC, after a median follow up of 21.6 months[329]. However, recent randomized trials of surgery alone versus surgery combined with oxaliplatin based HIPEC for 30 min at 42°C failed to show efficacy of the addition of HIPEC, either in the treatment or in the prevention of PM[330–332]. As a result, the value of HIPEC for colorectal cancer regarding optimal choice of drug, HIPEC temperature and treatment duration are under debate[333], even including the role of the raised temperature[334].

3.2.3. Isolated perfusion

Equipment: Prophylactic hyperthermic isolated limb perfusion (ILP) is applied for treatment of localized high-risk melanoma and soft tissue sarcoma in extremities[335, 336]. ILP involves placement of intraluminal vascular catheters in the inflow and outflow vessels of the extremity, which are then connected to an extracorporeal flow circuit to circulate heated chemotherapeutics for 60–90 min. An upstream tourniquet compresses collateral vessels to fully isolate the extremity. An advantage of ILP is the ability to use higher drug doses, thus locally enhancing efficacy of chemotherapy in the limb while avoiding systemic side effects. By using the vascular system for heat delivery, the temperature rise is inherently uniform. All the equipment required consists of standard equipment already in use for standard surgical care (tourniquet, catheters, heart-lung machine).

Clinical applications of isolated perfusion: This very effective treatment approach may avoid the need for amputations. A multicenter non-randomized trial combining tumor necrosis factor (TNF) with 60–90 min melphalan-based ILP for treatment of locally advanced soft tissue sarcomas in extremities reported response rates above 70% and limb salvage rates above 80%[336]. For ILP mild temperatures of 38–39°C are essential to obtain a good response without damage to the normal tissues in the limb. Higher temperatures (42–43°C) increase the response rate, but are also associated with very severe normal tissue toxicity[336].

3.3. Whole body hyperthermia

Equipment: During whole body hyperthermia (WBH) the body core temperature is increased to 39–40°C for 6 hours (fever range WBH)[337] or to 41–42°C for 60 min

(extreme WBH) [35, 338]. WBH is usually applied in combination with systemic therapy, for treatment of metastatic disease. Insulation of the body is required to avoid heat loss. During extreme WBH the patient is under sedation or even general anaesthesia. Several systems have been developed to apply WBH using radiant heat. Current commercially available WBH systems use infrared radiation and include the Iratherm1000 (Von Ardenne GmbH, Dresden, Germany) and the Heckel HT3000 (Hydrosun Medizintechik GmbH, Müllheim, Germany) systems. Both devices use water-filtered infrared A and are capable of providing a safe, well controlled and fairly homogeneous temperature elevation[338]. Extra-corporal perfusion and convective WBH techniques have also been applied, but these tended to be associated with higher levels of toxicity and have been abandoned in favor of radiative WBH techniques[338].

Clinical applications of whole body hyperthermia: Phase I/II clinical trials have been performed for e.g. ovarian cancer, colorectal adenocarcinoma, lung cancer and sarcoma and studies report serious grade 3/4 toxicity, of which myelosuppression is most common[35]. Absence of phase III trial results makes the additive value of WBH as part of palliative or curative care unclear. Less demanding treatment options are usually preferred. Ongoing research is investigating the potential benefit of WBH in combination with immunotherapy[13] as well as for non-malignant diseases[339].

4. Treatment control

Treatment control is important for ensuring high quality hyperthermia treatments. For all non-conductive hyperthermia techniques the steady state tumor temperature distribution achieved during hyperthermia depends on the balance between heat generated in the tissue by the hyperthermia device, and heat removed by thermal conduction, blood flow in discrete large vessels and perfusion in small vessels. Heat generation and removal are both difficult to predict accurately due to uncertainty in the dynamic and patient dependent tissue and perfusion properties. At hyperthermic temperatures, perfusion is significantly increased in the heated region as a result of physiological temperature regulation mechanisms in the body. The magnitude of this increase is dynamic and on forehand unknown and depends on the local temperature and other factors[340]. Therefore temperature feedback combined with treatment planning are needed to generate the desired temperature distribution. In this section we briefly discuss the role of thermometry and treatment planning for achieving treatment control for the devices presented in this review.

4.1. Thermometry

Adequate temperature control is crucial in clinical hyperthermia in view of the strong dose-effect relationship of hyperthermia both for achieving optimal therapeutic gain[3, 268, 341] as well as for avoiding side effects in normal tissue[342, 343]. Thermometry is performed to this end with either single or multi-sensor probes in or near the target volume, or non-invasively by external thermometry methods. Invasive temperature probes provide the gold standard (except with ultrasound where viscous artefacts give unpredictable results) and are based on different measurement principles, including thermocouples, thermistors and fiber-optic sensors. A method is selected based on its appropriateness, including compatibility

with the hyperthermia methods, used as outlined in reviews and guidelines[344, 345]. The metal leads of thermocouple probes require attention as they may cause local interference and erroneous read-outs when combined with EM and US based hyperthermia devices[346–348]. When thermocouple thermometry is combined with MR thermometry the metal leads may cause field inhomogeneities resulting in critical MR signal voids. Fiber-optic probes are generally insensitive to electromagnetic interference, but are mechanically fragile and can be disturbed when used during US or laser-based hyperthermia. A major limitation of probes is their invasive nature, which is not always feasible.

Non-invasive thermal monitoring would be ideal, and for very superficial skin tumors real-time non-invasive infrared thermography can provide 2-D temperature maps, this thermometry method measures the infrared energy of the patient and converts this to temperature. Infrared thermometry is standardly used in combination with the contact-free infrared hyperthermia treatment using the Hydrosun system (Hydrosun medizintechnik GmbH)[228]. For 3D thermal monitoring, CT, MR and US based non-invasive thermometry methods have been developed[345, 349–351], but presently these do not provide the same accuracy as thermometry probes. A major drawback of CT thermometry is the ionizing radiation issue, which makes that MR and US-based methods are generally preferred. When applying MR-thermometry, proton resonance frequency shift (PRFS) methods are preferred because of the excellent linearity and temperature dependence of the PRF[349]. Qualitative US ablation monitoring, which targets tissue coagulation and bubble formation is feasible and robust US thermometry exists for temperatures above 50°C[345]. Several ultrasound acquisition strategies are employed in ultrasound thermometry and ablation monitoring. For example, changes in stiffness monitored with US shear wave imaging are indicative of cellular necrosis[352].

Non-invasive thermometry is less challenging and often clinically used for thermal ablation monitoring, where a relatively low temperature resolution suffices to detect a temperature rise as this rise is much higher (10 – 40 °C) than for hyperthermia devices (1 – 6 °C). Therefore, applications for mild hyperthermia are still limited and particularly preferred for tumor sites where placement of invasive probes bears significant clinical risks, bearing in mind the pitfalls of the presently available MR or US based non-invasive thermometry methods when used in the mild hyperthermia temperature range. Although US methods have made significant progress for thermometry in this range[345], noninvasive PRFS-based MR-thermometry is most frequently used[353]. This method can provide reference-based temperature maps in near-real time. Under favorable, low blood flow conditions an accuracy of ~1°C can be achieved, but the method is sensitive to field drifts and susceptibilities and significant artefacts can occur due to movement, e.g. in the presence of high blood flow, breathing, cardiac and bowel motion, limiting the number of appropriate tumor locations[345, 349, 354]. These issues all need to be compensated for, for accurate temperature mapping. MR-guided hyperthermia works well for large fixated tumors (especially soft tissue sarcoma)[355]. Since MR-thermometry requires a trade-off between spatial and temporal resolution, acquisition is often limited to representative tissue slices to reduce acquisition times and allow online control. Practical methods for on-line optimization of the temperature distribution achieved with locoregional hyperthermia with MR-thermometry feed-back are still under development[285].

For scanned focused ultrasound treatments, US guidance offers fast imaging with the benefit of immediately revealing obstacles in the acoustic beam path, while MR provides high contrast soft tissue images suitable for planning. Furthermore, since MR allows the acquisition of near-real time temperature information, this can be used to establish a feedback system to the ultrasound driving electronics[356, 357]. The closed-loop feedback can be used either to achieve or to maintain a given target temperature or to deliver a predefined thermal dose. This provides better lesion control as it can compensate real-time for local differences in ultrasound absorption or heat loss due to perfusion. Recently, a model predictive control algorithm in combination with MR temperature mapping was introduced for a voxel-based heating strategy that allows compensation for local heat losses e.g. due to perfusion with a high spatial resolution[39]. MR thermometry finds now routine use in all MR-HIFU applications[358, 359].

Based on these useful clinical applications, heating devices such as HIFU or RF antennas have been integrated into MR scanners to allow temperature mapping[285, 360]. Commercially available MR guided devices which incorporate MR-thermometry sequences include the BSD-2000 sigma-eye which can be integrated into the MR systems of various vendors (see section “Locoregional heating techniques”), as well as the Sonalleve HIFU system integrated into the 3T Achieva MR system (Philips) and the ExAblate FUS system integrated into the Discovery MR450w 1.5T wide bore and Discovery MR750w 3.0T wide bore MR systems (GE). US guidance is clinically used in combination with ablative SFUS devices; the Sonablate[361] and Ablatherm[362] systems, where feedback is based on changes in echogenicity rather than temperature mapping[363] (see also section ”Local heating techniques: scanned focused ultrasound”).

4.2. Treatment planning

Treatment planning simulates SAR distributions and/or temperature patterns in the patient to visualize the effect of different treatment strategies[364]. This can be very helpful in assisting in treatment control. The prediction of SAR and temperature distributions is clinically helpful, even though well-known dependencies on patient models and tissue properties remain. Therefore, quantitatively reliable prospective treatment planning of SAR distributions is challenging and quantitative prediction of temperature is even more challenging because of the uncertainties in tissue properties, and a lack *a priori* in knowledge of the dynamic changes in perfusion levels which occur during heating[364–367].

Treatment planning is therefore still a research tool for most heating techniques, or is under development for relatively new techniques such as MNP, IRE and HIPEC[368–372]. For thermal ablation, treatment planning can be especially helpful to predict the size of the ablation zone when the target region is located close to critical structures or large cooling blood vessels which can affect the ablation zone[373]. Recent research focused on 3D planning of image-guided RFA by means of interactive access path determination based on optimization[374]. A first retrospective study indicated that this approach has the potential to improve the classical RFA planning based on inspection of 2D images alone[374]. Software-guided RFA of primary and secondary liver tumors is currently evaluated in the ClinicIMPPACT study; a multicenter-, prospective-, non-randomized clinical trial to

evaluate the accuracy and efficiency of innovative planning and simulation software[375]. MWA has the potential of creating larger ablation zones compared to RFA, but at the same time this yields a greater risk of thermal damage in surrounding healthy tissues, which explains the research interest in development of personalized MWA treatment planning[376]. However, the ultimate planning of MWA is still based on clinical experience of the physician. Characterization of dielectric and thermal property changes and tissue shrinkage are essential for the development of numerical predictive tools.

An additional challenge for reliable hyperthermia treatment planning is the fact that dielectric tissue properties change significantly during treatment in the ablative temperature range[377]. To improve the robustness of treatment planning predictions for ablation, application of probabilistic modelling techniques is presently investigated[378]. For most anatomical locations (with exception of the brain) treatment planning for ultrasound is very challenging since full-wave 3D simulations are extremely computationally intensive, and thus it is mostly used to optimize or adapt the aperture of US phased arrays to the tumor location or shape[379, 380]. Treatment planning for HIFU has to some extent become obsolete because of the use of on-line MR-thermometry for treatment guidance.

Significant progress has been made in the development of treatment planning for classical electromagnetic superficial and locoregional hyperthermia, where the integration into the clinical workflow is becoming common practice[364]. Treatment planning can be very useful for applicator selection to determine a treatment strategy[27, 381] or to evaluate potential for heating[280, 382]. Despite the limited quantitative reliability, treatment planning can help to optimize heating patterns for locoregional phased array systems. A cross-over trial comparing treatment planning-guided steering and steering with empirical steering guidelines demonstrated that steering guided by treatment planning is feasible[383]. Since measured and simulated changes in SAR and temperature resulting from phase and amplitude adjustments during hyperthermia treatments correlate[384, 385], adaptive treatment planning was further evaluated to be used on-line to determine alternative antenna settings that suppress hot spots, or to improve tumor heating during treatment. The practical use of treatment planning to improve treatment control has been demonstrated during clinical hyperthermia treatments[34, 355, 386, 387]. Furthermore, ongoing research aims to quantify the radiosensitizing effect of hyperthermia in terms of equivalent radiation dose, i.e. the radiation dose yielding the same biological effect as the combination of radiotherapy and hyperthermia. Results from biological modelling applied to prostate cancer[388], cervical cancer[389], and recurrent paediatric sarcoma[390] patients demonstrated substantial dose escalations of typically 10 Gy by adding hyperthermia. Biological modelling can also be useful to answer clinically relevant research questions such as the optimal timing between radiotherapy and hyperthermia[271]. Thermoradiotherapy planning is feasible and important to optimize hyperthermia combined with radiotherapy in individual patients[391].

5. Future perspectives

As demonstrated in this review, a large number of hyperthermia and thermal ablation devices have been developed, which are routinely and successfully used for a variety of tumor indications. Progress has resulted in many dedicated devices designed to meet specific

heating requirements for specific tumor sites. The hyperthermia field has progressed from single source hyperthermia applicators to sophisticated multiple source instruments. Successful clinical trials have been conducted which combined hyperthermia with radiotherapy or chemotherapy. In some cases, the hyperthermia devices possessed limited spatial control of the SAR distribution. Nevertheless, results demonstrated that the degree of control was sufficient for the tumor sites involved, which included bladder, superficial tumors and deep-seated pelvic tumors. Unmet clinical needs are progressing towards more challenging tumor sites such as brain, deep-seated head and neck tumors and peritoneal metastases[392–395]. As a result, there is a trend towards device designs providing greater spatial control of the energy deposition to ensure that SAR and temperature distributions in tissues reliably match with rigorous treatment plans to achieve effective treatment of challenging tumor sites, while sparing adjacent critical structures. Real-time 3-D temperature feedback data combined with reliable treatment planning to guide the applicator settings is also required to achieve the desired tumor target temperature distribution. Examples of this trend include development of dedicated MR guided hyperthermia applicators for brain tumors[393] and H&N tumors[256–258] based on MW technology, as well as US or MR guided HIFU devices, both for hyperthermia and for thermal ablation. A design challenge for most of these devices is matching the technical and clinical performance of the device with the oncological requirements for the specific site, e.g. the target volume size for gastrointestinal tumors and the need to spare surrounding normal tissue for brain tumors. For treatment planning, the use of validated and robust algorithms is important, which could possibly be standardized by defining established modelling and validation guidelines for development of software tools.

As shown in Figure 5, another clear trend over the past two decades is the steadily growing interest in almost all hyperthermic applications, but especially applications of thermal ablation techniques and the more recent rise of HIPEC. This trend is also evident in the increasing clinical application of specific forms of thermal ablation and hyperthermia as shown in Table 2. Thermal ablation is now more popular than application of hyperthermia as radiosensitizer or chemosensitizer, and the rapid rise of HIPEC and hyperthermic chemotherapy for NMIBC testify that combination of hyperthermia with chemotherapy is growing faster than combination of hyperthermia with radiotherapy, which is also associated with a different focus in device development. A breakthrough in heat-triggered tumor targeted drug delivery is one trend that would further strengthen popularity of the combination with chemotherapy[156, 162–165, 190]. Finally, the recent trend to combine thermal therapies with immunotherapies has demonstrated significant potential to address recurrence and metastasis in preclinical and clinical pilot studies[396–399]. When this is supported by further clinical evidence, a further growing interest in hyperthermic applications can be expected.

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6. References

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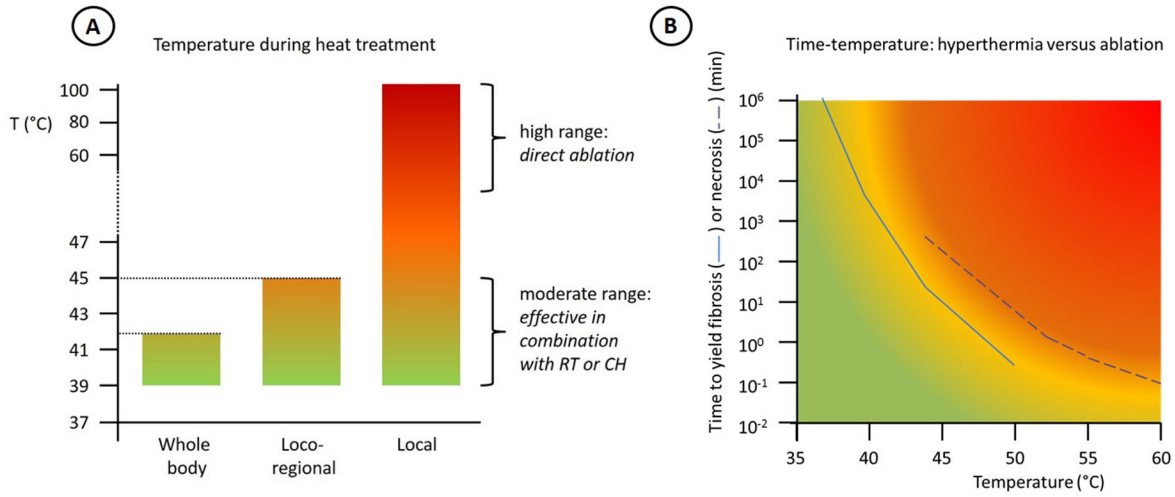

Figure 1:

A: Characteristics of the three main treatment approaches in terms of temperature level. B: Time to yield muscle fibrosis (continuous curve) or necrosis (dotted curve) at specific temperatures for hyperthermia and ablation (based on Dewhirst et al [20]).

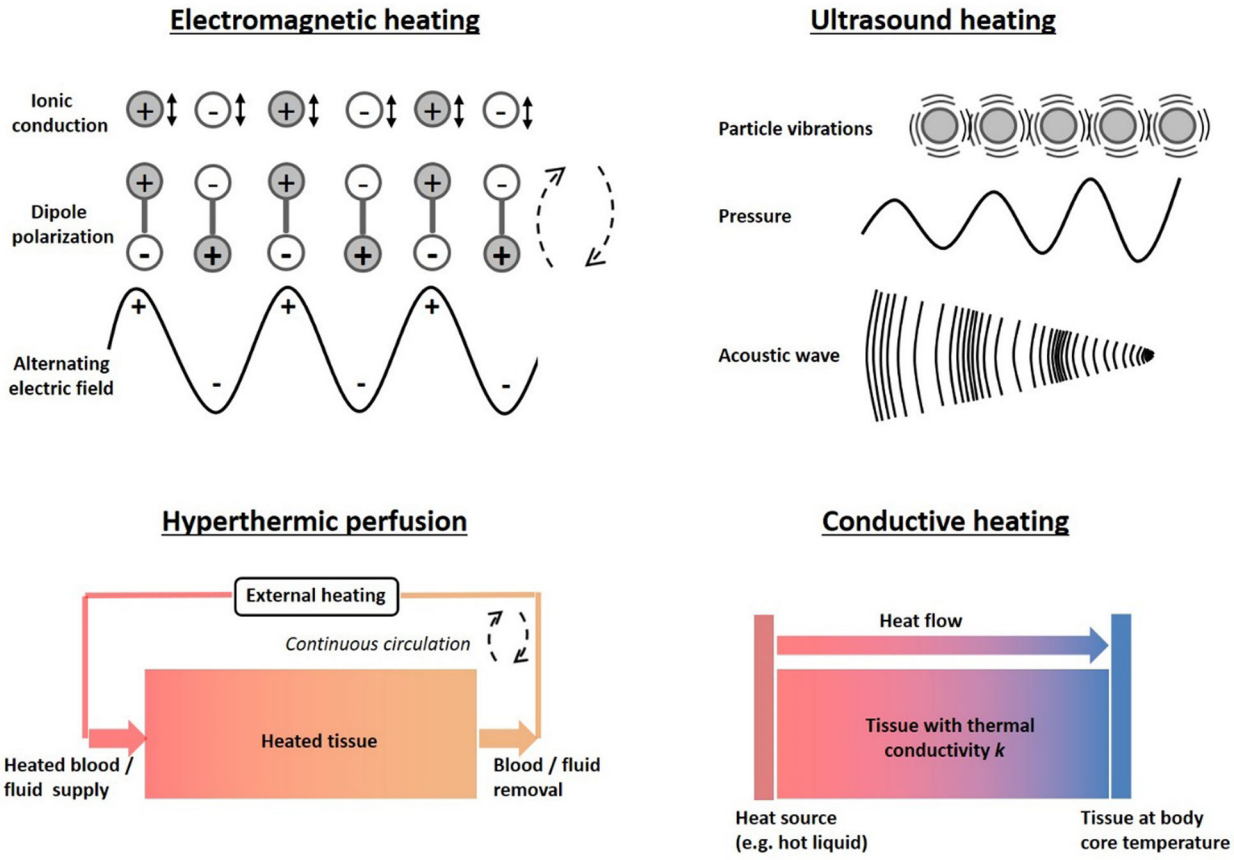

Figure 2:

Schematic representation of the heating mechanisms of different clinical heating techniques: Electromagnetic (i.e. capacitive, radiofrequency, microwave, infrared and laser heating), focused ultrasound, hyperthermic perfusion and conductive heating.

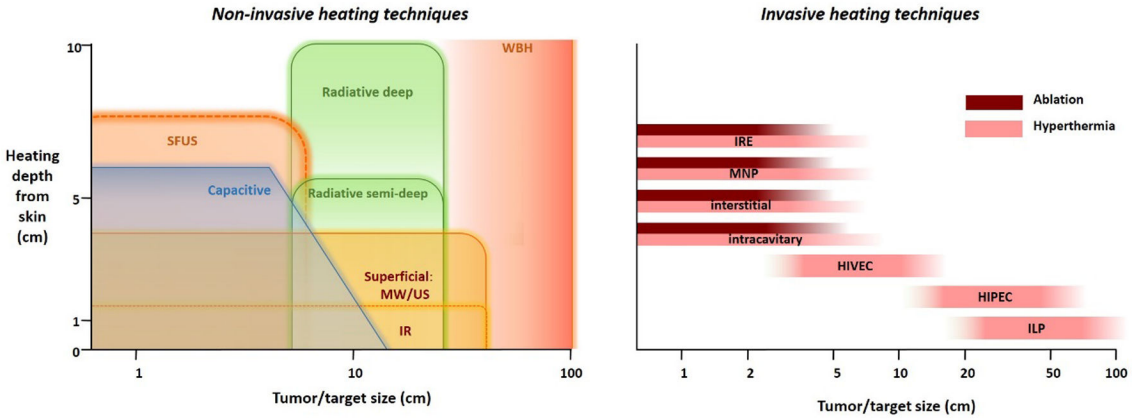

Figure 3:

Left: schematic overview of the heating depth from the skin and the tumor/target size that can be heated with various non-invasive heating techniques. Right: Schematic overview of the tumor/target size that can be heated with various invasive heating techniques.

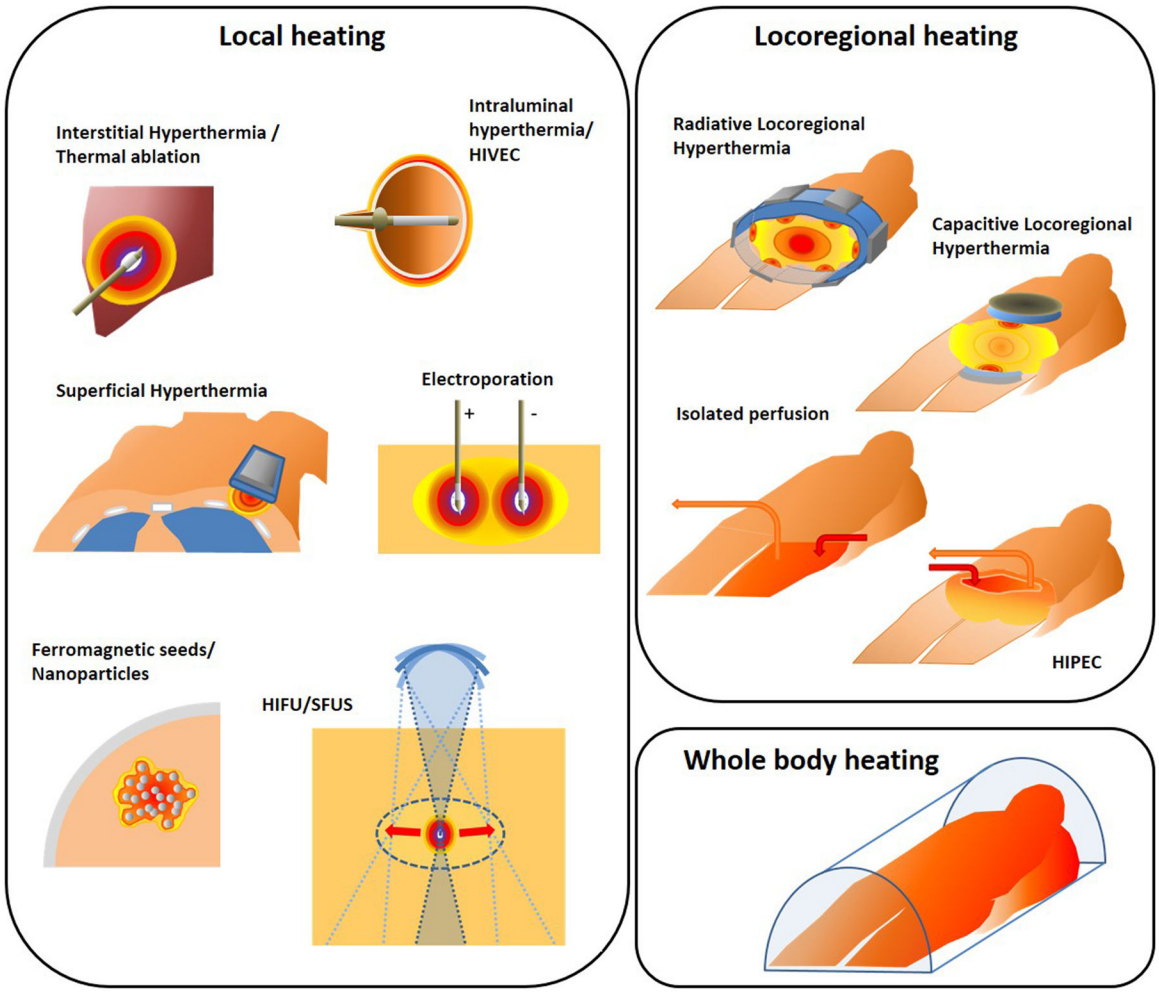

Figure 4:
Graphical representation of different heating techniques.

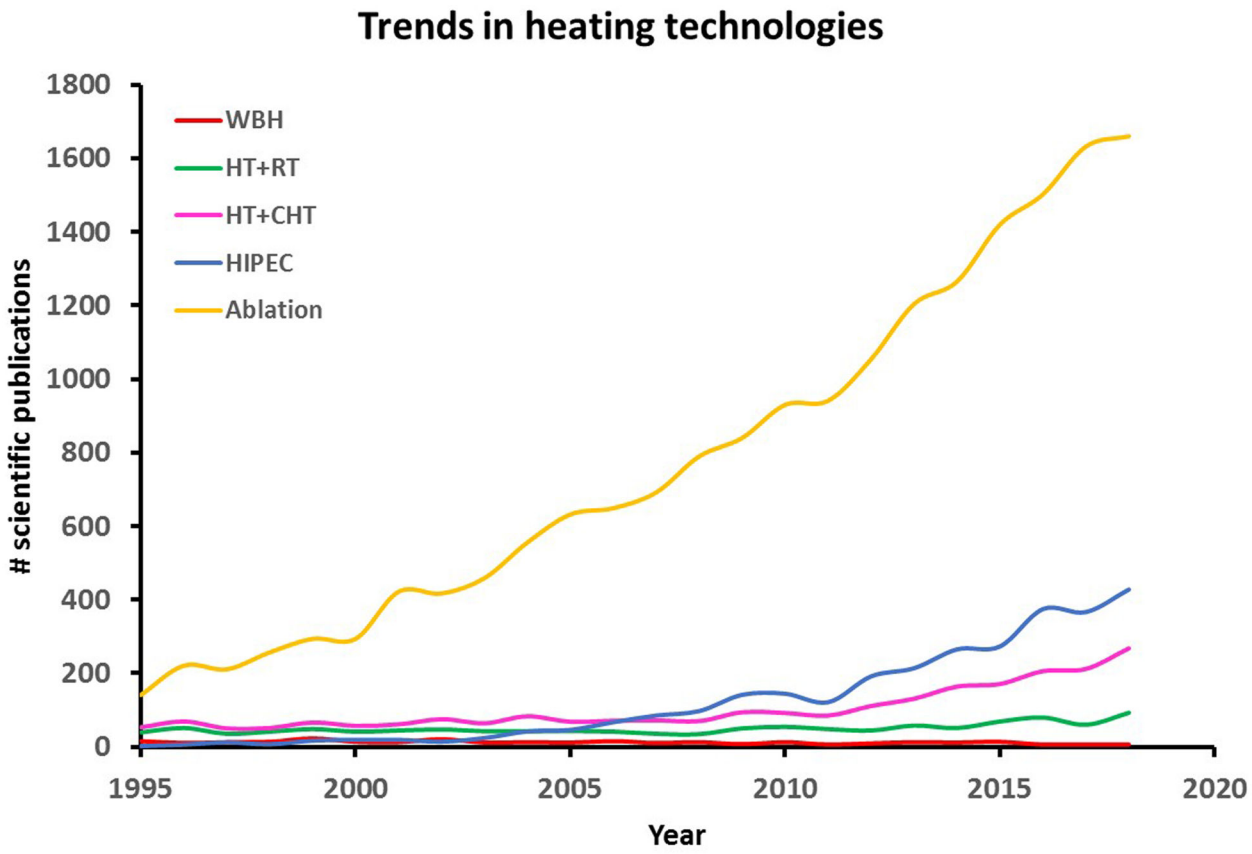

Figure 5:

Trends in heating technologies, represented by a rough estimate of the number of publications from 1995 till present on whole body hyperthermia (WBH), hyperthermia combined with radiotherapy (HT+RT), hyperthermia combined with chemotherapy (HT +CHT), hyperthermic intraperitoneal chemotherapy (HIPEC) and thermal ablation. Search terms used in Web of Science were: (WBH OR whole body hyperthermia; (hyperthermia AND radiotherapy) OR thermoradiotherapy; (hyperthermia AND chemotherapy) OR thermochemotherapy; HIPEC OR Hyperthermic Intraperitoneal Chemotherapy; thermal ablation OR RFA OR MWA). NB: Although this search did probably not retrieve all relevant publications and some overlap is likely between topics (e.g. HT+CHT and HIPEC), this graph is indicative for the trends in interest for different heating techniques.

Table 1:

General summary of heating techniques, typical goal temperatures, treatment scheme and duration, as well as experimental (*italic*) and clinically proven applications.

protocol	Synergizing with	Technique		Temperature range (^{0}C)	Duration session (min)	Number of sessions & frequency	Tumor sites: Proven/ routine *experimental*	refs
Hyperthermia as sensitizer	Chemotherapy	Local	IHT	39–45	60	1–12 sessions before, during or after chemo		
			SFUS	39–45	30–60		***LI***	[190]
			MNP	39–45	60			
			Intraluminal	39–45	60		**BL**, ***RE***	[221–224, 400, 401]
			Capacitive	39–45	60		***HN***	[402]
			Radiative	39–45	60			
		Locoregional	Capacitive	39–45	60		***BL***, **CE**, ***LI***, ***LU***, ***OE***, ***PA***	[31, 295–297, 301, 305–308, 403–405]
			Radiative	39–45	60		***BL***, ***CE***, **EX**, ***LI***, ***OE***, ***PA***, ***PE***, **PO**	[311–315, 392, 406–412]
			HIPEC	40–43	30–90	1 session during chemo	**PE**	[327–329, 332]
			ILP	38–39	60–90	1 session during chemo	**EX**	[335, 336]
		WBH		39–42	60–120		***LU***, ***PA***, ***PO***, ***RE***	[35]
	Radiotherapy	Local	IHT	39–45	60	1–5 sessions, 1x/2x weekly during RT, before/after RT fraction	**BR**, ***HN***, ***PR***	[90, 117, 119, 413]
			SFUS	39–45	60		***PR***	
			MNP	39–45	60		***BR***, ***PR***	[214, 414]
			Intraluminal	39–45	60		***OE***, ***RE***	[400, 415, 416]
			Capacitive	39–45	60		***CW***, **HN**,	[269, 417, 418]
			Radiative	39–45	60		**CW**, **HN**, ***IB***, **ME**,	[253, 254, 257, 265, 267, 268, 419, 420]
		Locoregional	Capacitive	39–45	60		***BL***, **BO**, **CE**, ***LI***, ***LU***, ***OE***, ***PA***, ***PR***, ***RE***	[292–294, 296, 298, 299, 301–305, 309, 421–423]
			radiative	39–45	60		***BL***, **CE**, ***OE***, ***LI***, ***PA***, ***PR***, **RE**	[272, 406, 410, 412, 424, 425]

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protocol	Synergizing with	Technique		Temperature range (^{0}C)	Duration session (min)	Number of sessions & frequency	Tumor sites: Proven/ routine *experimental*	refs
Thermal ablation	n.a.	Local	IHT	50–100	<5	1 session	***BO, BL, BR, HN, IB,* LI, *KI*, LU, OE, *PA*, PR, TH**	[110, 121, 122, 124, 125, 127–142, 144, 145, 147, 149–151, 426]
			SFUS	50–100	<5		**BO, *BR*, CE, *IB, LI, KI, OE, PA, PO*, PR, *TH***	[78, 81, 95, 138, 154, 167–169, 171–182, 184, 185, 187, 188]
			IRE	50–100	<10		***KI, LI, LU, PA, PR***	[201–206]

BL: bladder, BO: bone (metastases, osteoid sarcoma), BR: brain, CE: cervix/uterus, CW: chest wall, EX: extremities, HN: head&neck, IB: intact breast, KI: kidney, LI: liver, LU: lung, ME: melanoma, OE: oesophagus, PA: pancreas, PO: pelvis other (soft tissue sarcoma/ pediatric tumors), PE: peritoneum, PR: prostate, RE: rectum, TH: thyroid.

Table 2:

Overview of clinical applications of local, locoregional and whole-body heating techniques. Open circles represent explorative (small/few phase I/II) use and solid black circles represent many/large phase I/II trials, retrospective analyses or phase III evidence.

	Local hyperthermia and ablation										Locoregional hyperthermia				WBH	
	IHT		SFUS		IRE	MNP		Intraluminal	Superficial		EM Locoregional		HIPEC	ILP		References
	HT	ABL	HT	ABL	ABL	HT	ABL		cap	rad	cap	rad				
BL: Bladder		○						●			○	○				[55, 149, 216, 217, 221–224, 272, 300–302, 407, 408, 427]
BO: Bone (metastases, osteoid osteoma)		○		●							●					[121, 171, 309]
BR: Brain	●	○		○			○									[80, 118–120, 145, 147, 148, 154, 214]
CE: Cervix/Uterus				●							○/●	●				[31, 167–170, 272, 307, 308, 310]
CW: Chest wall									○	●						[228, 232, 263–266, 417, 418]
EX: Extremities												●		●		[311, 335, 336]
HN: Head & Neck	○	○							●	●/○						[130–133, 257, 269, 413, 419, 420]
IB: Intact breast		○		○						○						[136, 180, 253, 254]
KI: Kidney		○		○	○											[134, 135, 184, 201, 428]
LI: Liver		●	○	○	○						○	○				[50, 104, 106, 107, 112, 124, 125, 139, 143, 144, 190, 201, 204, 305, 306, 412]
LU: Lung		●			○						○				○	[103, 108, 127–129, 140–142, 206, 292–297]
ME: Melanoma										●						[267, 268]
OE: Oesophagus		●		○				○			○	○				[122, 137, 185, 404, 405, 410, 415, 423, 426]
PA: Pancreas		○		○	○						○	○			○	[138, 179, 201–203, 315, 403, 406, 422]
PE: Peritoneum												○	●			[320, 322–325, 327–329, 392, 411]
PO: Pelvis other: soft tissue sarcoma/ pediatric tumors				○								●			○	[181, 182, 311–314]

	Local hyperthermia and ablation							Locoregional hyperthermia					WBH	References
	IHT		SFUS		IRE	MNP	Intraluminal	Superficial		EM Locoregional		HIPEC	ILP	
	HT	ABL	HT	ABL	ABL	HT	ABL		cap	rad	cap	rad			
PR: Prostate	○	○/●		●	○	○					○	○			[78, 81, 90, 95, 117, 150, 151, 172–178, 205, 298, 299, 414, 424, 425]
RE: Rectum							○				○	●		○	[35, 272, 303, 304, 400, 401, 416]
TH: Thyroid		●		○											[130–133, 187]