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ULTRASOUND HYPERTHERMIA TECHNOLOGY FOR RADIOSENSITIZATION

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Abstract

Hyperthermia therapy (HT) raises tissue temperature to 40–45°C for up to 60 minutes. Hyperthermia is one of the most potent sensitizers of radiation therapy (RT). Ultrasound-mediated HT for radiosensitization has been used clinically since the 1960s. Recently, magnetic resonance-guided high-intensity focused ultrasound (MRgHIFU), which has been approved by the United States Food and Drug Administration for thermal ablation therapy, has been adapted for HT. With emerging clinical trials using MRgHIFU HT for radiosensitization, there is a pressing need to review the ultrasound HT technology. The objective of this review is to overview existing HT technology, summarize available ultrasound HT devices, evaluate clinical studies combining ultrasound HT with RT, and discuss challenges and future directions.

Keywords

Ultrasound; hyperthermia; radiotherapy; radiosensitization; cancer; MRgHIFU; MR thermometry

INTRODUCTION

Hyperthermia therapy (HT) refers to the procedure of raising tissue temperatures to 40–45°C for various lengths of time (up to 60 min) (Emami et al. 1992; Hurwitz and Stauffer 2014; Wust et al. 2002). HT is different from thermal ablation. Thermal ablation rapidly heats cancerous tissue to temperatures >60°C, which are sufficient for coagulative necrosis (Chu and Dupuy 2014). In contrast, HT is not intended to produce substantial cell death directly. There have been efforts to treat tumors with HT alone over the years; however, HT is most often used in combination with other therapeutic modalities including chemotherapy and radiation therapy (RT). HT has been successfully used as a sensitizer for chemotherapy in the treatment of various solid tumors (Hurwitz and Stauffer 2014; Issels et al. 2010a;

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Conflict of Interest

The authors have no relevant financial interest to disclose.

Wessalowski R, Kruck H, Pape H, Kahn T, Willers R, Göbel U 1998; Wessalowski et al. 2003; Wessalowski et al. 2013). Several reviews have summarized current understanding of HT synergistic effects with chemotherapy and outcomes from various clinical studies (Datta et al. 2015; Gao et al. 2016; van der Heijden and Dewhirst 2016). This review focuses on discussing the combination of HT with RT for cancer treatment.

HT is one of the most effective radiation sensitizers (Horsman and Overgaard 2007). At the beginning of the 20th century, William Coley observed that induction of fever by injecting patients with killed bacteria led to tumor regression (Coley 1910). Clinical studies from the 1990s until current have demonstrated that HT could interact synergistically with ionizing RT to improve tumor control and survival rate, as summarized in several reviews (Datta et al. 2015; Horsman and Overgaard 2007; Mallory et al. 2016; Rao et al. 2010). By the end of the last century, there was a dampening in the enthusiasm for HT in clinical practice mainly due to a lack of proper heating and temperature monitoring techniques (Bakker et al. 2018). Since the beginning of this century, there has been a resurgence of interest in HT because of the development of reliable HT applicators and adequate dosimetry using non-invasive magnetic resonance (MR) thermometry. MR thermometry is a noninvasive temperature monitoring technique based on MR parameters that are sensitive to temperature changes (Crezee et al. 2016b; Datta et al. 2016; Hurwitz et al. 2014; Winter et al. 2015). As of 2014, there were 109 clinical trials involving HT listed at ClinicalTrials.gov (Cihoric et al. 2015), and more recent trials have been summarized by (Mallory et al. 2016). The positive outcomes of numerous trials strongly support the rationale of using HT to improve the outcomes of RT in the clinic.

The evolution of ultrasound HT techniques up to the 20th century has been summarized in a review by Diederich and Hynynen (Diederich and Hynynen 1999). The current review presents advances in ultrasound HT devices to date, evaluates clinical studies on ultrasound HT radiosensitization, and concludes with a discussion of remaining challenges and future directions. It was written by performing an extensive bibliographic search associated with ultrasound-mediated HT and RT in PubMed using the following keywords: radiotherapy, hyperthermia, ultrasound hyperthermia, high-intensity focused ultrasound, and ultrasound. The references from selected studies were manually examined to identify relevant reports and summarized in this review. Clinical studies published after 1990 were considered only when those studies explicitly mention that informed consent was received from each patient and the study protocol was approved by the local ethics committee or institutional review board. This criterion was not used for clinical studies published before 1990, given that explicit mention of conformance to human study rules was not required in published works in those early years. For all pre-clinical studies cited, we only considered studies with approval by the appropriate institutional animal care and use committee or followed ethical research guidelines of their institutions.

MECHANISMS OF HT-INDUCED RADIOSENSITIZATION

The exact mechanisms for HT-induced radiosensitization are slowly revealed. As briefly described below, existing understanding of the underlying rationale of heat-induced radiosensitization includes HT impairment of deoxyribonucleic acid (DNA) repair caused by

RT, HT induced changes in the tumor microenvironment, and HT stimulation of immune response (Oei et al. 2017b; Peeken et al. 2017). More detailed discussions of the mechanisms are available in several reviews (Emami and Song 1984; Mantso et al. 2016).

Early studies concerning the mechanisms of HT-induced radiosensitization focused on the cellular consequences of combined treatments on DNA damage and its repair (Cohen et al. 1988; Kai and Hahn 1976). HT alone was found to neither lead to DNA damage by itself nor to increase the DNA damage induced by RT (El-Awady et al. 2001). Most studies concluded that the inhibition of the repair of RT-induced DNA damage by HT accounted for the synergistic interaction of HT and RT (Kaur et al. 2011; Van Oorschot et al. 2016). More recent studies have found that HT inhibits homologous recombination (Genet et al. 2013; Krawczyk et al. 2011; Oei et al. 2017a) and leads to the shunting of early DNA double-strand break repair to nonhomologous-end rejoining, which is more error-prone (Bergs et al. 2013). In other words, it has a higher possibility to encounter an error in the DNA repair process comparing with homologous end rejoining, which is essentially error-free. HT was recently found to inhibit many other types of DNA double-strand break repair (Oei et al. 2015), which suggested the possibility of using synthetic lethality, a type of genetic combination where the co-occurrence of two genetic events results in organismal or cellular death (Nijman 2011), to escalate the effectiveness of such inhibition (Eppink et al. 2012). The latter approach has been reported to be successful using poly (ADP-ribose) polymerase inhibitors (Oei et al. 2017a).

The tumor microenvironment plays an essential role in both tumor progression, metastasis, and therapeutic response (Trédan et al. 2007; Yang and Lin 2017) and alterations in the tumor microenvironment are a hallmark of cancer (Hanahan and Weinberg 2000). In the tumor microenvironment, persistent hypoxia formed due to a lack of oxygen diffusion in the highly abnormal tumor microvasculature and the failure of rectifying the oxygen insufficiency. Hypoxia leads to a lack of oxidation of DNA free radicals by O_2, thus causing the failure to induce DNA breaks, which is one of the main mechanisms of ionizing radiation affecting the tumor cells (Wilson and Hay 2011). Additionally, tumor hypoxia has been proved to drive the tumor to a more malignant phenotype and stimulating the tumor invasion and metastasis (Bussink et al. 2008). HT can rectify the hypoxia at both tissue and cellular levels (Vaupel and Kelleher 2010). At the tissue level, HT has been shown to increase blood flow and enhance tissue oxygenation, all of which improve the response of tissues to RT, as reviewed by Vaupel and Kelleher 2010 (Vaupel and Kelleher 2010). Increased blood flow also changes the pH in the tumor, which in turn sensitizes the tumor to HT [reviewed in (Peeken et al. 2017))]. These effects have been found in several clinical studies (Jones et al. 2004; Oleson 1995; Song et al. 1996). At the cellular level, HT has a greater effect on hypoxic cells than on aerated cells regarding cytotoxicity (Dewey et al. 1977; Harisladis et al. 1975) through the induction of mitochondrial damage and oxidative stress (Roti Roti 2008).

There is compelling evidence that HT can lead to activation of the immune system (Frey et al. 2012). HT induces heat shock proteins (Morimoto et al. 1997), some of which can activate both the innate and adaptive immune systems (Calderwood 2018; Pockley and Henderson 2018). Inhibitors of the most abundant heat shock protein 90 (hsp90) lead to

radiosensitization, and a subset of soft-tissue sarcomas that express elevated levels of hsp90 was associated with poor prognosis, arguing for the use of such inhibitors in the clinic (Ernst et al. 2015). Another important effect of hypoxia that has been elucidated recently is the suppression of the anti-tumor effector cells and the enhancement of the escape of the tumor from immune surveillance (Lee et al. 2010). Several studies have shown that such immune suppression can be reversed by HT (Lee et al. 2010). RT has also been shown to affect the host immune system both locally and systematically (Weichselbaum et al. 2017). RT promotes the release of cytokines that recruit antigen presenting cells into the tumor microenvironment, leading to the activation of the cytotoxic T-cell function. The interaction of these immunological consequences of RT with HT has been reviewed in the context of using high-intensity focused ultrasound (HIFU) heating for radiosensitization (Cirincione et al. 2016).

In addition, there are other critical mechanisms related to HT-induced radiosensitization, including tumor thermotolerance and vascular thermotolerance, both of which should also be taken into considerations when designing clinical trials. Tumor thermotolerance refers to that one HT session may cause a temporal heat resistance in the tumor cells against subsequent HT (Overgaard and Nielsen 1983)(Overgaard and Nielsen 1983). The vascular thermotolerance means that two HT sessions with an interval of within 48 hours can substantially increase the blood flow compared with a single HT (Griffin et al. 2010; Song et al. 2001). The vascular thermotolerance is of great significance because they can potentially be utilized to improve tumor oxygenation for up to 2 days after the application of one HT session. Both of these two mechanisms have an impact on the designing of clinical studies because an optimal time interval between sequential HT sessions can be found, below which adding more HT sessions may improve tumor oxygenation for the radiosensitization; while above which additional HT may have little beneficial effects on RT response. Multiple HT in a row is still advantageous for clinical hyperthermia when they are separated by a few days because thermotolerance decays back to baseline thermosensitivity after a few days (Kamura et al. 1982). It was recommended that HT treatment should be given only twice per week to remove effects of thermotolerance (Dewhirst et al. 2005).

HT TECHNIQUES

HT techniques typically fall into three categories: whole-body, local, and regional (Van Der Zee 2002). Whole-body HT is typically used to treat metastatic disease by heating the entire body of patients using physical modalities, such as heated air, heated water, infrared chamber, heated blankets, and extracorporeal blood-warming (Gyp et al. 2017; Short and Turner 1980). Local HT is generally used to treat solid, localized disease at or near the surface of the skin or natural body orifices (Datta et al. 2015; Gao et al. 2016). Regional HT is generally used for diseases in deeper tissues (Longo et al. 2016). One approach to deep-seated tumor heating has been applying technologies used for external local heating at regional levels. Another approach has been inserting specially designed sterile probes through body cavities for intracavitary heating. The heating techniques are often characterized as superficial or deep, or as external and internal (Stauffer 2005). The route of application various for different methods. Superficial heating is normally achieved using devices outside the body. Non-invasive deep tissue heating uses extracorporeal devices to

delivery energy deep into the body without any surgery. Intracavitary HT is achieved using miniature heat sources situated within the lumen or body cavities. Physical means for induction of local/regional HT include hot water, radiant heat (visible and infrared), capacitive/inductive radiofrequency, microwaves, ultrasound, and magnetic field heating of nanoparticles (Baronzio et al. 2014; Das et al. 2019; Short and Turner 1980; Spirou et al. 2018). All these techniques are derived from three basic physical mechanisms for delivering heat energy to the body (Stauffer 2005): (1) Thermal conduction of heat (heat flows from higher to lower temperature), such as using hot water and infrared chamber; (2) Resistive or dielectric losses from an applied electromagnetic field, such as radiofrequency waves and microwaves; (3) Mechanical losses due to molecular collisions from an ultrasound pressure wave. The clinically applicable devices for inducing the HT have been summarized in previous publications (Baronzio et al. 2014; Ryan and Brace 2017).

Local/regional HT in the clinic is delivered mainly by microwave (100 MHz to 3 GHz electromagnetic wave), radiofrequency waves (500 kHz to 15 27 MHz electromagnetic waves), or ultrasound (300 kHz to 10 MHz mechanical waves). Other techniques are either little-used or in the developmental stage, such as magnetic nanoparticle heating (Dan et al. 2015). Low-frequency electromagnetic waves with the wavelength vary from about 4 cm to 200 cm in “practical” frequency range (such as microwaves and radiofrequency waves) can penetrate deep into the body (1–15 cm as typical aperture-to-tumor distance) but are difficult to focus. Focusing can be achieved at higher frequencies for microwaves and radiofrequency waves; however, absorption at higher frequencies prevents adequate tissue penetration. As a result, electromagnetic waves-based techniques are mostly limited to treating superficial tumors or regional heating of deep sites (Diederich and Hynynen 1999). Ultrasound, which is a mechanical wave, provides an alternative technology for generating heat through mechanical friction, which has the unique advantages of having adequate tissue penetration at wavelengths that permit beam shaping and focusing. The penetration depth of the ultrasound can be adjusted from less than 1 cm up to about 20 cm (Sethi and Chakarvarti 2015), which allows ultrasound to treat both superficial and deep regions. The disadvantages of ultrasound include high bone absorption and unable to penetrate through tissues that contain air (e.g., respiratory tract and gastrointestinal tract).

In parallel to the development of HT techniques, the development of strategies to detect temperature changes induced by HT is also critical. Thermometry has been a rate-limiting challenge for the more widespread clinical adoption of HT (Mallory et al. 2016). Early methods of thermometry require insertion of thermometers into the tumors, which are invasive, cumbersome, and only provide information at a few points (Bakker et al. 2018; Datta et al. 2015). In the recent few years, there is an expanding interest in integrating HT with MR thermometry. Thermometry techniques used in HT are summarized in a later section. The integration of ultrasound HT with MR thermometry has been implemented in commercially available MR-guided high-intensity focused ultrasound (MRgHIFU) systems. MR thermometry provides real-time, noninvasive, volumetric temperature measurements. Feedback control algorithms based on MR thermometry have been implemented for on-line controlling of the HIFU output. MRgHIFU has the great potential to overcome the long-standing challenge in HT: localized and homogeneous heating of the tumor within an exact temperature range for a precise period of time.

THERMAL DOSIMETRY

With the development of HT for the treatment of cancer in conjunction with RT, thermal dosimetry is of great importance. CEM43, which represents cumulative equivalent minutes at a temperature of 43°C is currently recognized as the most commonly used dosimetry parameter (Chicheł et al. 2007). CEM43 is a normalized parameter to convert various time-temperature exposures to equivalent exposure time in minutes at a reference temperature, 43°C. There are limitations of CEM43 as it is originally designed to predict tumor cell death based on the direct cell kill of HT alone, which is generally not the main therapeutic action of HT in synergy with RT (Spirou et al. 2018; van Leeuwen et al. 2017). Nevertheless, there is a fair body of evidence that CEM43 works reasonably well as a measure for thermal dose (Dewey 2009; Dewhirst et al. 2005; Pearce 2013). Other thermal dose parameters have also been used, such as T_{90}, T_{50}, and $T_{10,}$ which stand for the temperature exceeded by 90%, 50%, and 10% of the intra-tumor measured points, respectively. These parameters lack integrated information over time. Parameters that combines CEM43 and T_x (i.e., T_{90}, T_{50}, and T_{10}) were also used, such as CEM43T90 which calculates an equivalent treatment time with T90 equals to 43°C (Hurwitz and Stauffer 2014).

The quality assurance (QA) or quality assessment of heating, which aims to assure the clinical HT being satisfactorily delivered to all patients in a given protocol, has evolved in the past three decades. The earliest QA requirements for hyperthermia was published in a paper dated back to 1984. That paper suggested applying HT until the maximum temperature measured by a set of sensors reaches about 40°C, after which reducing the power to permit thermal equilibrium (Nussbaum 1984). The challenges in early days HT QA were reported by the Radiation Therapy Oncology Group (RTOG). These challenges included less optimal heating in larger lesions (>3 cm) and the limited ability of invasive thermometry to accurately characterize the temperature distribution in a tumor (Perez et al. 1989). Recently provided QA guidance for clinical studies specified that the general objective is to avoid temperatures exceeding 43°C in normal tissue and heat HT targeted tissue to 44°C for 60 min (Bruggmoser et al. 2011). Recent research used temperatures in the range of 39–43°C to achieve the concomitant oncological therapeutic effect and at the same time minimize the cytotoxicity to normal tissues (Crezee et al. 2016a; Dewhirst et al. 2005). The latest QA guideline published in 2017 (Trefná et al. 2017) specified that the minimum thermal dose requirement for superficial HT of tumors extending from skin to cutaneous tissue layers is to reach T90 of 40°C for 1 hour and T50 exceeding 41°C throughout the target volume with the maximal normal tissue temperature of 43–45°C.

IMAGE GUIDANCE TECHNIQUES

In the recent few years, there is an expanding interest in integrating HT with temperature imaging techniques. Several non-invasive, real-time temperature imaging techniques have been developed based on MR (Rieke and Butts Pauly 2008), ultrasound (Lewis et al. 2015), photoacoustic (Yao et al. 2013), and X-ray computed tomography (Fani et al. 2014). MR thermometry is the only clinically-available modality for non-invasive, real-time, volumetric, and quantitative temperature measurement (Rieke and Butts Pauly 2008). A detailed review

of various thermometry techniques can be found in a recent report by Lewis et al. (Lewis et al. 2015). Here we briefly summarize the progress in MR thermometry for HT guidance.

With the advent of MR thermometry about two decades ago, many MR thermometry methods have been developed. The most commonly used method is based on temperature sensitive proton resonance frequency shift (Winter et al. 2015). The rationale of this method is that the magnetic field at each voxel shows excellent linearity and sensitivity with the temperature-induced changes in proton-electron screening in the temperature range of hyperthermia if neglecting the magnetic volume susceptibility (Hindman 1966; Poorter et al. 1995). Thus, by measuring phase changes at each voxel, the relative temperature can be derived from the electron screening of proton in the application of non-adipose tissue (McDannold 2005; Peters et al. 1998; Sprinkhuizen et al. 2010). The most prevalent challenge for the proton resonance frequency shift-based MR thermometry is motion-induced phase artifacts. This motion includes physiological motion (e.g., respiratory, cardiac, and digestive-related motion) and bulk tissue motion.

Extensive studies were performed to evaluate the performance of MR thermometry. A group at Duke University performed earlier work on assessing the potential of MR thermometry in hyperthermic oncology and found the uncertainties of MR thermometry ranging from 0.3°C to 1.4°C (1 standard deviation) within a 40 s scan time for monitoring HT induced by a diffusing laser fiber inserted into ex vivo porcine liver (Clegg et al. 1995)(Clegg et al. 1995). Carter et al. (Carter et al. 1998) demonstrated the feasibility of performing MR thermometry during HT of patients with sarcoma in the lower extremity. Gellermann et al. (Gellermann et al. 2006) performed MR thermometry in patients with high-risk soft tissue sarcomas of the lower extremities and pelvis during regional HT and found a significant correlation between pathohistological response (defined as a necrosis rate>90%) and standardized thermal parameters such as CEM43T90. Craciunescu et al. (Craciunescu et al. 2009) compared MR thermometry with invasive temperature measurements in patients with extremity sarcomas during HT by a radiofrequency applicator and found an excellent correlation between noninvasive MR thermometry and invasive measurement. Lam et al. (Lam et al. 2015) evaluated the performance of MR thermometry for monitoring MRgHIFU ablation treatment (duration up to 2 min) of patients with bone metastases in the upper body and pelvis. They found the average temperature variation for the MR thermometry was higher in the upper body as compared to the pelvis.

The integration of ultrasound HT with MR thermometry has been implemented in commercially available MRgHIFU systems. MR thermometry provides real-time, noninvasive, volumetric temperature measurements. Feedback control algorithms based on MR thermometry have been implemented for on-line controlling of the HIFU output (Enholm et al. 2010; Partanen et al. 2012). Recently, our group evaluated the performance of MR thermometry in healthy volunteers at different anatomic sites (chest wall, bladder wall, and leg muscles) for long scan times (30 min and 60 min, V. V. N. Kothapalli et al. 2018). We found that only the leg muscles had mean precision and accuracy <1°C as the leg muscles had the lowest motion-induced artifacts in MR thermometry when compared with the chest wall and bladder wall. Reliable MR thermometry is achievable for relatively stabilized tumors such as sarcoma in extremity and recurrent rectal carcinoma (Chu et al.

2016), but moving organs in the upper abdomen are still challenging. Further development of temperature-sensitive MR sequence is strongly needed to compensate motion artifacts, as well as other challenges, such as tissue heterogeneities, temperature-dependent tissue changes, and perfusion(Wust et al. 2016) (Wust et al. 2016).

ULTRASOUND HT TECHNOLOGY

According to the design of ultrasound transducers, we can divide the evolution of ultrasound HT devices into four generations: (1) The 1st generation: single, unfocused, piston transducers in conjunction with temperature measurements using a single thermocouple; (2) The 2nd generation: arrays of separately controllable stationary or static transducer arrays in combination with multiple thermometers for temperature monitoring; (3) The 3rd generation: mechanical scanning of ultrasound beams; (4) The 4th generation: focused ultrasound transducers that integrate mechanical scanning and electronic beam steering, combined with noninvasive, real-time, volumetric MR thermometry. The ultrasound HT technology can also be categorized based on the location of the applicators into external, intratumoral, and intracavitary techniques. In the following, we describe several selected ultrasound HT devices as examples to demonstrate the advantages and limitations associated with ultrasound technology used for HT. These examples are not meant to be inclusive as many devices have been developed throughout the history (Diederich and Hynynen 1999). It needs to note that ultrasound thermal ablation systems share some common features as the ultrasound HT devices; however, this review focuses on the HT devices.

The 1st generation clinical ultrasound HT device used a single element unfocused piezoelectric ultrasound transducer of 1–3 MHz in frequency (Marmor and Hahn 1978). The transducer was covered by a flexible membrane of Mylar or latex and directly placed on the skin over the tumor. The skin was cooled by circulating cold water through the transducer housing. The temperature was measured by a thermocouple inserted in the center of the superficial tumor. A large number of similar ultrasound HT systems were manufactured. Those systems were simple to construct and operate. The energy deposition pattern was well collimated and relatively uniform power output could be obtained over the whole surface of the transducer. The main advantage of the 1st generation systems was the simple design and manufacturing. The major limitation was the lack of spatial and temporal control of the heating.

The 2nd generation devices were developed in the 1980s, which used separately controllable stationary or static transducer arrays in combination with multiple thermometers for temperature monitoring. Compared with the 1st generation systems, the 2nd generation devices had the main advantage of better spatial and temporal control over the energy deposition. An example of this system is Sonotherm 1000, a commercial system designed with either a 4- or 16-element ultrasound array (Benkeser et al. 1989; Ogilvie et al. 1990; Underwood et al. 1987). This system was approved by the United State Food and Drug Administration (FDA) in 1989. It is the first, and the only FDA approved ultrasound HT device, and it is still in use nowadays in the clinic. This applicator can be operated at 1 MHz for heating deeper regions (3–6 cm) or the third harmonic of 3.4 MHz for more superficial sites (2–3 cm). The power level of each element can be individually controlled during

treatment to modify the temperature distribution in response to heterogeneous and dynamic tissue-heating properties, as well as patient discomfort. Normally, 2–16 needle thermocouples are inserted into the tissue to monitor temperature and provide feedback control for each transducer element's output (Dunlop et al. 1986; Singh et al. 2004; Straube et al. 1996; Xia et al. 2001). The limitations of the Sonotherm system include that the applicators are heavy and bulky and setting up the system is time-consuming (Samulski et al. 1990)(Samulski et al. 1990). A clinical study obtained temperature data from 31 patients who underwent a total of 147 HT sessions with the Sonotherm system and found its ability to achieve 42°C minimum tumor temperature for 60 min is limited (Samulski et al. 1990). The proportion of treatment with a space-time-average temperature ≥ 42°C was only 19% in this patient group.

Different from the first two generation devices which consist of static or stationary ultrasound transducers, the 3rd generation systems were characterized by the addition of mechanical scanning of the ultrasound beams (Moros et al. 1995; Moros et al. 1996; Moros et al. 1997; Novák et al. 2005; S.Shimm et al. 1988). The mechanical scanning was achieved through two different strategies: (1) mechanically scan an acoustic reflector while keeping the ultrasound transducer stationary and (2) mechanically scan the ultrasound transducer itself. The first strategy was evident in the scanning ultrasound reflector-linear array systems (SURLAS) developed in the 1990s by Moros et al. at the Washington University in St. Louis (Moros et al. 1995; Moros et al. 1996; Moros et al. 1997). The SURLAS system was configured with a linear ultrasound array (frequency ranging between 1.0–5.0 MHz) positioned at the side of the applicators outside the RT field. The ultrasound energy was directed from the arrays toward a scanning acoustic reflector that redirected the ultrasound energy into the target volume. This system enabled the acoustic waves and the RT beams to enter the targeted volume from the same direction simultaneously. Temperature elevations inside the targeted volume were dependent on the array size, operating frequency, reflector scanning motion, thermal properties of tissue, and blood perfusion. A dual-array system utilizing parallel-opposed linear ultrasound arrays with different frequencies and a double-faced (V-shaped) scanning reflector was later proposed for improving the penetration depth control by varying the excitation magnitude of one array relative to the other (Moros et al. 1997). A software was developed to run the SURLAS system and coordinate the output power of the therapy applicator to achieve a proper and safer operation, (Novák et al. 2005). The software can divide the applicator's treatment window into 64 sectors with a dimension of 2 cm for each sector and control the power of each sector independently to adjust the power deposition in three dimensions. Simultaneously, the software could log the monitored temperature from the thermocouples and terminate the treatment in case of a malfunction in any part of the system or a violation of a safety criterion (Novák et al. 2005). SURLAS were unique in that they allowed simultaneous delivery of HT and RT, but they carried the limitation that temperature fluctuations were observed, which was caused by the cyclical motion of the scanning reflector. The second strategy was evident in the scanned focused ultrasound system (SFUS), which mechanically moves the transducer to improve temperature uniformity throughout the tumor volumes (S.Shimm et al. 1988). Typical SFUS systems included four to six spherically focused transducers, and they were aligned to form a common focal zone of a few millimeters in diameter. The focal zone was mechanically

scanned within the tumor following circular or octagonal patterns (Diederich and Hynynen 1999). SFUS achieved a high degree of spatial control of power deposition patterns by controlling the operating frequency and applied power levels as a function of location to account for variations of tumor thickness. This high degree of spatial control of power deposition offered a solution to compensate for temperature variations due to tumor irregularities, perfusion heterogeneity, and the presence of blood vessels (Lele 1989). Thermocouples with small diameters (e.g., 25 to 125 microns) were used for temperature measurements and feedback control (Lele 1989). The SFUS system was used in multiple clinical trials for the treatment of brain tumors after craniotomy was performed (Guthkelch et al. 1991), as well as tumors in breast, superficial sites, and within the pelvis (Hand et al. 1992). These work on SFUS were the critical body of work that formed the basis for the development of the 4th generation ultrasound HT devices, MRgHIFU, as discussed below.

The 4th generation of ultrasound HT radiosensitization devices started to emerge in the 1990s. These devices comprised of HIFU phased array transducers integrated with MR imaging, commonly known as MRgHIFU. MRgHIFU devices were originally designed and currently used in the clinic primarily for thermal ablation treatments. HIFU has the ability to rapidly heat up the target tissue to an ablative temperature in a very precise manner and sparing the surrounding normal tissue and MR thermometry can monitor the temperature in real time non-invasively. About 30 ongoing clinical trials on MR-guided FUS were summarized in a recent publication (Rodrigues et al. 2017), most of which aim for ablation or thermal surgery. These devices can also be modified to incorporated HT capabilities (Hijnen et al. 2012; Salgaonkar et al. 2017). Profound (formerly Philips) MRgHIFU system has incorporated HT into its Sonalleve system. As far as we know, this is the only MRgHIFU system that has been commercially available for HT application. The system is equipped with a 256-channel phased-array transducer (radius of curvature of 70 mm, focal length of 140 mm, frequency of 0.8 MHz and 1.2 MHz). The transducer is housed inside the patient table and connected with an electromechanical positioning system to deliver spatially and temporally controlled heating. This system can generate heating cells with different sizes: 18 mm, 32 mm, 44 mm, and 58 mm (Tillander et al. 2016). MR imaging is used for treatment localization, real-time temperature mapping and feedback control of the HIFU treatment, and posttreatment evaluation of the treated tissue. A binary feedback control algorithm based on MR thermometry has been implemented to turn on/off the HIFU output to achieve homogenous and precise volumetric heating. The system also features a direct skin cooling (DISC) device consists of a water cooling reservoir which is mounted on top of the patient tabletop above the acoustic window of the HIFU transducer and directly in contact with the patients' skin. The temperature of the water cooling reservoir is regulated at constant room temperature (20°C), such that the temperature is well tolerated on bare skin(Ikink et al. 2015) (Ikink et al. 2015). Preclinical studies using pigs have shown the feasibility and safety of the MRgHIFU HT, and clinical trials are currently ongoing (Chu et al. 2016). With the advent of MRgHIFU HT technology, ultrasound HT is entering a new era with unprecedented flexibility and precision in volumetric temperature control, although further research is warranted to develop and evaluate this technique.

Currently, it has been demonstrated in preclinical studies that MRgHIFU HT allows focal heating of tissue to well-defined temperature under MR image guidance. MRgHIFU HT has

been successfully used in hyperthermia-triggered local drug delivery in combination with temperature-sensitive nanoparticles loaded with chemotherapy agents to enhance the local delivery of the chemotherapeutic into liver tumor, pancreatic tumors, and glioblastoma in preclinical studies (De Smet et al. 2011; Farr et al. 2017; Hijnen et al. 2014; Hijnen et al. 2017; Ranjan et al. 2012). MRgHIFU has been used in a clinical study for HT of 10 patients with inoperable recurrent rectal adenocarcinoma, and in all three patients who completed the treatment, MRgHIFU-induced HT was safely delivered (Chu et al. 2018). Our group at the Washington University in St. Louis has been working on obtaining an investigational device exemption from the FDA for starting the first clinical trial in combining RT with MRgHIFU HT in the United States. As an emerging clinical application of MRgHIFU HT for radio-sensitization, there is the need to summarize the literature on the clinical studies of ultrasound-induced HT and guide the development of this emerging field.

CLINICAL STUDIES OF ULTRASOUND-INDUCED HT

Over the past few decades, clinical studies have shown that the use of ultrasound HT is an effective adjuvant to RT for improving tumor control and response rates. Therapies combining ultrasound HT with RT have shown efficacy in the treatment of different types of tumors. Here we summarize clinical studies in the treatment of head and neck, breast cancer, prostate cancer, cancer in the pelvis, and central nervous system malignancies. More than half of the studies included more than one type of cancer. We organized the clinical studies based on the disease type that had the largest patient population. Table 1 summarized clinical studies included in this paper regarding the treatment site, RT dose, HT device (generation 1-4 is shorten to G1-G4), HT temperature, HT duration (D), HT session (S) numbers, treatment efficacy, and treatment toxicity. The clinical outcomes considered were: (1) Complete response (CR), defined as complete disappearance of the treated tumor; (2) Partial response (PR), defined as greater than or equal to 50% reduction in tumor volume.

Head and neck cancers

Ultrasound-mediated HT combined with RT has been explored for the treatment of superficial sites located in the head and neck. Previous studies evaluated the efficacy, safety, and thermal parameters correlated with the treatment outcome and concluded that ultrasound-mediated HT combined with RT was well-tolerated with minimal cytotoxicity and increased long-term benefit compared to RT alone.

The therapeutic efficacy of combined ultrasound-mediated HT and RT for head and neck cancer treatment has been consistently demonstrated in multiple trials. Woeber (Woeber 1960) reported that combined treatment of X-ray therapy and ultrasound HT of superficial tumors obtained the same therapeutic results (no principle differences in the reaction of the tissue or the subsequent healing process) as that achieved by the classical X-ray therapy with one third less radiation dose. However, this earlier trial is limited in that no thermometry was used to measure thermal treatment parameters.

Thermal parameters related to tumor response were also analyzed. A more recent trial confirmed the correlation between adequate thermal dose and complete tumor response using a non-focused ultrasound array system, Sonotherm 1000 (Xia et al. 2001). It found

that intra-tumoral cumulative equivalent minutes of over 42.5°C could be an important thermal parameter for predicting tumor response. Kapp et al. (Kapp et al. 1990) conducted a prospective randomized trial that compared the tumor response after two versus six total HT sessions as adjuncts to RT and showed no statistically significant differences in tumor response between the two versus six HT populations (p=0.89). When used as an adjunct to RT, neither the number of HT sessions performed per week nor the number of sessions in total were found to influence the treatment outcome, which could be associated with thermotolerance.

Breast and chest wall cancers

We found several studies that analyzed the correlation between thermal parameters and CR rate for breast cancer treatments with RT combined with HT (RT+HT). One study compared the efficacy of the combination of RT and HT, RT alone, and HT alone in a phase I/II study (Dunlop et al. 1986) and showed that adequate HT (CEM43 >20min for more than one session) combined with RT reached a higher CR rate of 86% compared with RT alone (35%, $p<0.001$) or RT with inadequate HT (35%, $p<0.001$). HT was performed post RT, either “immediately” (15–20 min) or 4 h later, usually twice per week with successive heat sessions separated by at least three days. Dunlop et al. (Dunlop et al. 1986) demonstrated that tumors receiving RT and effective HT had higher complete response rate than those received RT with inadequate HT ($P<0.001$), indicating that sufficient heating is critical to the success of the RT+HT. However, a phase I/II clinical trial reported a conflicting conclusion that increases or decreases in CR rate were not associated with any examined treatment factors, including interval between initial diagnosis and first failure, prior radiation, prior chemotherapy, prior hormonal therapy, treatment site, current radiation dose, hyperthermia technique, number of hyperthermia treatment, and chemotherapy agents (Bornstein et al. 1993). However, this conclusion was limited by the small number of patients (29 patients) included in this study. In a prospective randomized clinical trial with 122 patients enrolled, Jones et al. (Jones et al. 2005) used cumulative equivalent minutes at 43°C exceeded by 90% of monitored points within the tumor (CEM43 T90) as a measure of thermal dose and found a thermal dose more than 10 minutes of CEM43T90 confered a significant local control benefit (measured by the duration of achieved local control) in patients with superficial tumors (including chest wall cancer) receiving RT(Jones et al. 2005). Although HT was given using the microwave instead of ultrasound, this landmark paper highlighted the significance of rigorous thermal dose prescription and administration. As for the minimal number of hyperthermia sessions required for local control without complications, a phase III clinical study (Emami et al. 1992) showed no significant difference in CR between HT fractionation of once per week and twice per week. These results agreed with the results reported by Kapp et al. (Kapp et al. 1990), both of which demonstrated that the number of HT every week caused no difference in the CR rate.

Studies were also performed to identify parameters predictive for complications of treatment, such as maximum tumor temperature, cumulative thermal dose, and the number of HT sessions. Reported safety issues associated with HT included superficial burns at the location of thermocouple insertion, pain during HT, increased cutaneous reactions to RT in the heated area, and desquamation reactions (Marmor and Hahn 1980). A phase I clinical

trial (Kapp et al. 1992) enrolled 124 patients and performed 249 HT sessions. The range of the maximum temperature for all treatments is 38.3–54.1°C. The average percentage of temperature within the tumor higher than 43.5°C is 43.5±25.0%. It found statistically significant correlations between the development of complications and multiple parameters, including (1) the average of the T_{max} in tumors, (2) the average percentage of recorded tumor temperature higher than 43.5°C (47.6% and 34.1% in the cases with and without complications, respectively, p=0.0071), and (3) the average number of HT courses (3.79 of the cases with complications and 3.03 of the cases without complications, p=0.038). This study also found the correlation between the maximum temperature achieved in tumors with the rate of complication in both acute and chronic toxicity. For complications which can heal within one month, the T_{max}≤42.5°C correlated to a low rate of complication of blistering (9.1%) and 42.6°C≤ T_{max}≤43.9°C correlated to an increased frequency of blistering (53.6%). For chronic complications, this study showed that burns requiring one month to heal did not appear when T_{max}<44°C but developed in 55.6% of the tumors when T_{max}≥44°C. In another respective study (Bornstein et al. 1993), the likelihood of complications and the total radiation dose was reported to have a statistically significant association. Another stage II-III clinical trial (Varma et al. 2012) performed 4–8 sessions of simultaneous thermoradiotherapy and studied the relationship between toxicities and treatment factors. They demonstrated that there was no relationship between above 2-grade morbidity and either total thermal dose or a total number of HT sessions (4 or 8), but there was a trend that the addition of HT to RT led to a greater late chest-wall morbidity compared with the RT alone.

Prostate Cancer

Prostate cancer was mostly treated with transrectal ultrasound hyperthermia in combination with RT. The effectiveness of RT+HT has already been demonstrated by the improvement of the disease-free survival rate (Algan et al. 2000; Fosmire et al. 1993; Hurwitz et al. 2002; Hurwitz et al. 2005; Hurwitz et al. 2011). A phase II clinical study compared the survival rate of RT+HT combined with androgen suppression therapy (AST) and AST alone in patients with prostate cancer (Hurwitz et al. 2011). The results showed that the 2-year disease-free survival rate (84%) improved significantly by RT+HT compared with the survival rate (64%) of similar patients on the 4-month AST. However, another phase I/II study administered RT concurrently with HT to a temperature of 42.5°C for 30 minutes for the treatment of patients with locally advanced prostate carcinoma (Algan et al. 2000). It found that there was no significant improvement in treatment outcome by RT+HT when compared with other studies reported in the literature evaluating external beam radiation therapy with or without androgen suppression.

As for the evaluation of complications, it was consistently found that RT+HT were well-tolerated with limited gastrointestinal toxicity in both short and long terms. In patients with trans-perineal thermometer catheter placements, mild hematuria occurred in 5/22 of the patients, while moderate hematuria occurred in 2/22 of the patients (Fosmire et al. 1993). As for the evaluation of gastrointestinal toxicity, two studies have been performed (Hurwitz et al. 2002; Hurwitz et al. 2005). A phase II study applied RT ± AST with 2 HT sessions to assess the rectal toxicity of HT+RT in treating prostate cancer. Results showed that the

multi-modality treatment-induced gastrointestinal toxicities were limited to Grade 2 (Hurwitz et al. 2005). Rectal toxicity correlated with average rectal wall T_{max}, and average prostate T_{max}. Later, the same team verified that both short- and long-term gastrointestinal toxicity were limited to grade 2. Acute grade 2 proctitis was correlated with a rectal wall temperature of over 40°C. Late gastrointestinal and genitourinary toxicity was not associated with the allowable rectal wall temperature. No late grade 3 or greater toxicities occurred (Hurwitz et al. 2005).

Cancers of the pelvis

Cancer in the pelvis could be treated with both intracavitary and external ultrasound HT devices. Intracavitary HT could be applied with high-dose-rate brachytherapy implants during RT in the treatment of cervical cancer. These catheter-based ultrasound devices provide a method to deliver 3D conformal heating integrated with high-dose-rate brachytherapy. Several publications have characterized the theoretical heating patterns to improve implantation strategies for these devices (Wootton et al. 2011b; Wootton et al. 2011a), but only one study performed HT using intracavitary catheter-based ultrasound applicator (Diederich et al. 2011). In that study, 100% of treatments achieved a goal of >60 min heating duration. No adverse events or toxicities in surrounding regions were observed. This study demonstrated endo-cervical ultrasound applicator could provide conformal and selective therapy, deliver efficacious temperatures and thermal dose (CEM43 calculated based on thermocouple measurements) to targeted volume, and reduce bladder and rectum exposure.

As for the external application of ultrasound for treating pelvis tumor. Harari (Harari et al. 1991) reported that RT combined with HT led to CR in 22% of the treated tumors, partial response in 40% of the treated tumors, dramatic local pain reduction in 42% of the treated tumors, and 83% of the complete responders remaining disease free for up to 12 months. In the annual meeting of the Society of Thermal Medicine in 2018, an on-going phase-I clinical trial of MRgHIFU HT as an adjuvant to RT and chemotherapy was reported (Chu et al. 2018). In all ten patients enrolled with inoperable recurrent rectal adenocarcinoma, three patients who completed all HT sessions had no unintended tissue damages. The mean temperature of all three patients who completed all three HT sessions were 41.2°C, 42.3°C, and 41.8°C with CEM43 of 3.3, 41.3, and 17.7, respectively. Additional studies are still needed to evaluate the efficacy of the MRgHIFU HT.

Central nervous system malignancies

A small phase I clinical study reported by Guthkelch et al. demonstrated the feasibility of ultrasound-mediated HT combined with RT for the treatment of primary malignant tumors of the brain (Guthkelch et al. 1991). Fifteen patients with a histological diagnosis of primary malignant tumors of a cerebral hemisphere received RT+HT repeatedly. A single-element focused ultrasound transducer was used to perform HT after a craniotomy, which avoided the attenuation of the ultrasound beam by the skull. The intra-tumoral temperature was measured by inserting thermal sensors, and the target temperature of 42.5°C was achieved at the tumor boundary by more than one point. Results showed that brain tumor HT was

feasible and therapeutic temperatures (≥42.5 °C) were achieved in approximately 50% of the measured points without unexpected toxicity (Guthkelch et al. 1991).

Melanoma

Two clinical studies published in 1982 revealed the increased efficacy when applying RT +HT compared to either modality alone. In one study (Corry et al. 1982b), the superficial tumors were heated to 43.5±0.5°C for one hour immediately before irradiation and found an overall response rate of 100% in RT+HT group compared with 30% in RT group and 50% in HT group. The other study (Corry et al. 1982a) found escalation of temperature was remarkably correlated with both the increased response rate from 53% (43-44°C) to 83% (48-50°C) and the increased duration of response (from 29 to 250 days for the same temperature increase).

CHALLENGES AND FUTURE DIRECTIONS

The ultrasound-mediated HT technology has been developed from stationary one size fits all planar transducers to site-specific conformal arrays generated by mechanical and electrical scanning of phased arrays. Thermal monitoring has evolved from recording at sparse, fixed locations using invasive thermal sensors to real-time, volumetric, noninvasive temperature monitoring using MRI. The real-time characterization of temperature changes in 3D provides feedback control of the ultrasound heating in 3D, bringing the possibility of achieving homogeneous heating of the tumor to an exact temperature range. Promising clinical results have been reported since the 1960s, which indicate that ultrasound HT has favorable effects as a radiation sensitizer in the treatment of cancer.

A better understanding of the ultrasound radiosensitization mechanisms is needed, although the mechanism for HT radiosensitization in general, regardless of the heating technology, has been studied for several decades. More work is needed to understand the potential unique mechanisms of ultrasound HT for radiosensitization. For example, although numerous studies have provided convincing evidence on the benefits of ultrasound HT combined with RT, we still need to better understand the synergistic interactions between ultrasound HT and RT. The mechanisms behind treatment enhancement effects induced by different ultrasound HT and RT sequence, time interval, thermal dose, and radiation dose are critical for establishing effective treatment protocols.

Besides understanding the mechanisms, ultrasound HT technology development remains to be the main challenge. Clinical HT trials have shown that most tumors are inadequately heated, and cold spots exist even in the most favorable cases (Overgaard 1989; Overgaard et al. 2009; Overgaard and Overgaard 1987). Although a minimum temperature of 41°C were claimed to be clinically feasible and tolerable for superficial tumors (Myerson et al. 1999), the temperature measured is not based on volumetric thermometry. Thus, a major effort must be made to measure the temperature throughout the tumor and to increase the fraction of target tissue heated to therapeutic temperatures (Diederich and Hynynen 1999). Before the recent introduction of MRgHIFU for HT, the clinical applications of ultrasound HT was limited by several technique challenges, such as the lack of real-time, noninvasive temperature measurement technology and difficulties in controlling the temperature in deep

tumors (Rao et al. 2010). One preclinical study in pigs has demonstrated the safety and feasibility of using MRgHIFU HT in the porcine leg muscles under real-time noninvasive temperature monitoring (Tillander et al. 2016). The MRgHIFU technique offers more control over the power deposition pattern, translating into better temperature distributions. Thus, one would expect that the clinical benefit of HT would also increase with this technique. Future efforts are needed toward improving the MRgHIFU HT technology, such as developing robust MR thermometry techniques and improving HIFU HT technique for fast and homogeneous heating. With the continued advancement of the MRgHIFU technology, extensive efforts are needed to push this new ultrasound HT technology toward regular clinical implementation.

The prognostic variables of HT in combination with RT need to be evaluated. Thermal dose parameters, such as CEM43 have been used as a predictor for treatment efficacy. Such thermal doses are originally defined based on the cytotoxicity effect of HT to cells, which has ignored other critical effects caused by HT and its synergy with RT (Van Rhoon 2016). However, clinical studies did report a significant correlation between the thermal dose such as CEM43 and treatment effect (De Bruijne et al. 2010; Dinges et al. 1998; Fotopoulou et al. 2010; Franckena et al. 2009; Issels et al. 2010b; Jones et al. 2005; Lee et al. 1998; Leopold et al. 1993; Overgaard et al. 2009; Rau et al. 2000; Sherar et al. 1997; Tilly et al. 2001; Van Der Zee et al. 1999; Wust et al. 1996). The MR thermometry technique will function as a propelling factor for the measurement of volumetric thermal dose. Extensive effort is still needed to develop volumetric thermal dosimetry method as prognostic variables for HT.

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Table 1

Clinical studies evaluating adjuvant ultrasound hyperthermia therapy combined with radiation therapy

Author Year	The site (# of patients or lesions)	RT[1] dose (Gy)	HT[2]					Treatment efficacy	Treatment Toxicity
			Device	Sequence	Temperature (°C)	Duration (min)	Session/wk; Session #		
Woeber 1960	Basal cell cancer (26 pts), squamous cell carcinoma (20 pts), malign melanomas (2 pts).	30–40 (4–6 Gy/fr, 7-8 fr)	G1[3]	Immediately pre-RT	NA	30–60	NA; 7-8	RT+HT: 33% decrease of RT dose compared with RT alone	Peculiar burning pain in regions where bone lying closely underneath
Xia 2001	Head & Neck (15pts), breast (9pts), lung (8 pts), esophagus (6 pts), colorectal (6 pts), soft tissue (5 pts), extremity (3 pts), other (2 pts)	40–70 (1.8–2.0 Gy/fr, 5 fr/wk)	G2	Post-RT, within 30min after RT	T(center)>42.5 °C for > 20 min in 55.4% cases.	60	2; 6–10	RT+HT: CR[4]:32.6%; PR[5]: 46.2%; No effect:21.1%	Hot sensation, pain, and blistering showed in most cases.
Emami 1992	Head and neck (40 lesions), chest wall (52 lesions), axilla (7 lesions), abdomen (2 lesions), pelvis (7 lesions), extremities (4 lesions), back (4 lesions), other (2 lesions)	6–115 (4Gy/fr, 2fr/wk, 4–5wks)	G1 & G2	Post RT, within 30-60min	CEM43[6] ≥ 15min achieved in 78% cases	NA	1 or 2; 1–18	RT+1 HT/wk: CR: 54.7%; Tumor control: 42% RT+ 2 HT/ wk: CR: 57.8%; Tumor control: 40% No sig. diff.	Severe soft tissue necrosis (18%).
Myerson 1999	Head and neck (21 pts), chest wall (15 pts), other trunk sites (7 pts), extremity (4 pts).	28–32 (2–4Gy/fr, 4fr/wk)	G2	Simultaneous	36% cases have CEM41[7]>60min.	45	1; 4–8	RT + HT: CR: 51%(1yr); PR: 17%(1yr).	Slow healing soft tissue ulcers required a median of 7 months to heal (21%).
Dunlop 1986	Adenocarcinoma at the breast (18 pts), adenocarcinoma at lung (1 pts), adenocarcinoma at stomach (1 pts), squamous carcinoma at lung (1 pts), squamous carcinoma at head and neck (2 pts), melanoma (4 pts), Kaposi's sarcoma (1 pts)	25–30 (2.5–3Gy/fr, 10fr)	G1	Post-RT, within 15-20min or 4h later	CEM43 ≥ 20min achieved in 58 cases	NA	NA; 1–4	RT only: CR: 35%. HT only: CR: 11%(P<0.05) RT+ HT: CR: 86%(P<0.05)	Termination during treatment due to pain and discomfort (9.09%); superficial blistering or burns arose around puncture sites
Bornstein 1993	Breast (29 pts; 39 lesions)	12–66 avg: 37; (2–4Gy/fr, 1–4fr/wk)	G2	Pre-RT, within 0.5-1h	Average T_{tumor}=41.2±1.7°C	53.9±7.9	1; 4–6	HT+RT+ chemotherapy: CR: 53% (10months)	Persistent ulceration of previously irradiated areas (67%); ulceration need surgical repair (38%).
Jones et al. 2005	Breast (70 pts); head and neck (14 pts); melanoma (11 pts); other (25 pts)	30–66 Gy for previously-irradiated lesions; 60–70 Gy for unirradiated lesions (1.8–2.0Gy/fr, 5fr/wk)	Microwave	Post-RT	Achieve thermal dose of 10 CEM43 T_{90}	1–2 hours	1 or 2; not reported	HT+RT: CR: 66.1%. RT alone: 42.3%. No overall survival benefit was seen.	Catheter complications (pain, infections, hemorrhages) (11%); thermal burns (25% of grade I; 16% of grade II; 5% of grade III).
Marmor and Hahn 1980	Multiple superficial metastatic sites (15 pts)	32–60 (2–4Gy/fr)	G1	Pre-RT for 15min and post-RT for 30min	T_{Skin} controlled below 43°C. Target T of tumor: 43°C.	45	NA	RT only: CR: 25%; PR: 25% RT + HT: CR: 100%	Increased cutaneous reaction to RT (13.3%); desquamated reaction (6.7%).
Kapp 1990	Head and neck, thorax,pelvis, extremities. (70 pts in total, without specify number of each disease)	21.6–66 (1.8–3.5 Gy/fr, 2–5 fr/wk)	G1 & G3	Post RT, within 30-45min	Intratumoral T: 40.2±1.2°C	45	1 or 2; 2 or 6	RT + 2 HT sessions: CR: 52%; PR: 7%(3wks) RT + 6 HT sessions: CR: 51%; PR: 9&(3wks) No sig. diff.	Skin depigmentation (24%); subcutaneous indurations/fibrosis (16%); tumor ulceration (9.1%); normal tissue ulceration (2.4%).
Kapp 1992	Superficial thorax (122 lesions), head and neck (47 lesions), extremities (27 lesions), deep head and neck (6 lesions), eccentric thorax (2 lesions), eccentric abdomen, superficial pelvis (10 lesions), eccentric pelvis (14 lesions), deep pelvis (25 lesions), eccentric extremity (1 lesions), deep extremity (1 lesions).	5.4–82.0	G1 & G3	Post RT, within 0.5-1h	Average T_{tumor}=42.0±1.3°C	45	1–2; 1-14	Maximum tumor temperature and number of treatments per field can predicate the development of complications in RT + HT.	Tumor ulcerations, infections, indurations and fibrosis, edema, persistent pain and late erythematous skin reactions, superficial (13.6%); deeply located (11.8%)
Varma 2012	Chest wall (57 pts)	46-50 (1.8–2Gy/fr)	G2	Simultaneous	All monitored thermometry more than ≥ 41°C for 0.5h	60	1 or 2; 4 or 8	RT + 4 HT sessions: disease recurrence rate: 30% (4yrs); RT + 8 HT sessions: No sig. diff.	Moist desquamation in the chest wall (43.86%); Grade2 morbidity (47.37%); Grade3 morbidity (14.04%); sensation abnormalities (29.82%); telangiectasias (17.54%); scaliness/roughness (3.50%)
Algan 2000	Prostate (23 pts)	50–68 (1.8–2.0Gy/fr, 5fr/wk)	G1 (TRUSH)	Simultaneous	T_{tumor}>42.5°C for at least 30 min	NA	1; 1–2	OS[9]: 73% (5yrs); Cause-specific survival rate: 79 % (5 yrs); Median survival: 36months; Biochemical no evidence of disease: 35% (5 yrs).	Perineal discomfort, urinary related, or more frequent bowel movements and diarrhea are the most common acute side effects. The duration of HT trended toward significance for OS (P=0.06).
Fosmire 1993	Prostate (14 pts)	67–70 (1.8–2.0Gy/fr, 5fr/wk)	G1 (TRUSH)	Simultaneous	CEM 42.5[10]>30min in 36% cases.	30	1; 1–2	RT and HT are well-tolerated and can consistently heat prostate gland.	Mild hematuria (22.73%); moderate hematuria (9.09%); treatment limited secondary to position intolerance and/or pain (9.09%).

Author Year	The site (# of patients or lesions)	RT[1] dose (Gy)	HT[2]					Treatment efficacy	Treatment Toxicity
			Device	Sequence	Temperature (°C)	Duration (min)	Session/wk; Session #		
Hurwitz 2002	Prostate (30 pts)	66.6±5% (1.8–2.0Gy/fr)	G1 (TRUSH)	Simultaneous	Mean T90 CEM43 is 7.3min.	39-80	1;2	Rectal toxicity of RT and HT correlates with maximum allowable rectal wall temperature.	Grade 2 Gastrointestinal (GI) toxicity (35.71%); the rate of acute grade 2 proctitis correlates with maximum allowable rectal wall T. No grade 2 GI toxicity observed.
Hurwitz 2005	Prostate (37 pts)	66.6±5% (1.8–2.0Gy/fr)	G1 (TRUSH)	Simultaneous	Mean T90 CEM43 is 8.4min.	39–80	1; 2	Grade 2 proctitis was greater for patients with T_{max} in rectal>40°C than patients with T_{max} limited to 40°C.	Acute grade 2 proctitis was greater for patients with an allowable rectal wall temperature of over 40.8°C.
Hurwitz 2011	Prostate (37 pts)	66.6±5% (1.8–2.0Gy/fr)	G1 (TRUSH)	Simultaneous	Mean T90 CEM43 is 8.4min.	39–80	1; 2	OS: 100% (2 yrs); 97.2% (4 yrs); 93.5 % (5-7 yrs).	Not reported.
Diederich 2011	Cervix (4 pts), prostate (3 pts)	NA	G1 (Catheter)	Simultaneous	T_{tumor}=40-45°C for 1h.	60	1; 1–2	Target temperature achieved without adverse events or toxicity observed.	No adverse events or toxicity associated with hyperthermia.
Harari 1991	Pelvis (22 pts), chest wall or breast (14 pts), neck (8 pts), axilla (7 pts)	10–76.4 (1.5–4 Gy/fr)	G3	Pre-RT, 10-30min	Intratumoral T_{min} ≥ 42.5°C for 0.5 h	30	1; 1–4	RT + HT: CR: 22%; PR: 40%; dramatic local pain reduction: 42%; disease free up to 1 yr in 83% of the CR.	Transient pain during HT (75%); superficial skin burns (10%); persistent skin blisters or burns (2.8%)
Guthkelch 1991	Brain (11 pts)	12–65 (5 fr/wk, the fraction dose depend on clinical situations)	G1	Pre-RT	Average $T_{tumor\ max}$=43.0±1.0°C	15–60	1; 2–4	RT+HT: 12-65 Gy. HT: 42.5°C at the boundary, 15-60 min/session, once per week.	Multiple infections (6%); Large areas of treatment-induced necrosis of tumor in all autopsied patients (33.3%).
Corry 1982a	Melanoma (11 lesions), adenocarcinoma in lung, cervix, ovary, or breast (7 lesions), sarcoma (2 lesions), squamous cell carcinoma (1 lesions).	24–40 (4 Gy/fr, 3fr/wk)	G1	Immediately prior to RT	Intra-tumor T=43±0.5°C	60	3; ≥6	RT only: PR + chemotherapy: 30% RT+HT: CR: 62%; PR + CR: 100% HT: CR: 10%; PR: 50%	Minimal with one case with sequelae.
Corry 1982b	Melanoma (10 pts), sarcoma (7 pts), squamous cell carcinoma in head and neck and lung (5 pts), adenocarcinoma in lung, breast, and renal (6 pts).	Not reported	G1	Post RT, time interval is not reported	T_{max}: 43~44°C in 21.43% cases; 45~47°C in 25% cases; 48~50 °C in 48% cases.	60	>6	RT + HT: CR + PR: 81% HT only: CR + PR: 41%	Treatment limiting pain relieved within minutes of the cessation of therapy (20%); skin blistering (13%).

1. HT: hyperthermia therapy.

2. RT: radiation therapy.

3. G: the generation of the ultrasound hyperthermia device

4. CR: Complete response, defined as complete disappearance of the treated tumor.

5. PR: Partial response, defined as greater than or equal to 50% reduction in tumor volume.

6. CEM43: Cumulative equivalent minutes reached 43°C.

7. CEM41: Cumulative equivalent minutes reached 41°C.

8. TRUSH: Transrectal ultrasound hyperthermia.

9. OS: Overall survival, defined as the length of time from the start of treatment for a disease that patients diagnosed with the disease are still alive.

10. CEM42.5: Cumulative equivalent minutes reached 42.5°C.