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Recent technological advancements in radiofrequency- and microwave-mediated hyperthermia for enhancing drug delivery

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ABSTRACT

Hyperthermia therapy is a potent enhancer of chemotherapy and radiotherapy. In particular, microwave (MW) and radiofrequency (RF) hyperthermia devices provide a variety of heating approaches that can treat most cancers regardless the size. This review introduces the physics of MW/RF hyperthermia, the current state-of-the-art systems for both localized and regional heating, and recent advancements in hyperthermia treatment guidance using real-time computational simulations and magnetic resonance thermometry. Clinical trials involving RF/MW hyperthermia as adjuvant for chemotherapy are also presented per anatomical site. These studies favor the use of adjuvant hyperthermia since it significantly improves curative and palliative clinical outcomes. The main challenge of hyperthermia is the distribution of state-of-the-art heating systems. Nevertheless, we anticipate that recent technology advances will expand the use of hyperthermia to chemotherapy centers for enhanced drug delivery. These new technologies hold great promise not only for (image-guided) perfusion modulation and sensitization for cytotoxic drugs, but also for local delivery of various compounds using thermosensitive liposomes.

Contents

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1. Introduction

Despite progress in cancer treatment outcomes, cancer mortality rates are rising because society faces an aging population. Patients that do survive after treatment, suffer longer from the severe side-effects induced by current aggressive treatments that often include radiotherapy, chemotherapy, or both. Hence, improvement of cancer therapy effectiveness is required while simultaneously reducing long-term side-effects. Extensive biologic research showed that hyperthermia therapy (HT) is a potent sensitizer of ionizing radiation and that HT can also greatly enhance the effectiveness of chemotherapy [1,2] as well as increase the tumor-specific immune surveillance [3,4]. Clinically, the beneficial impact of HT induced by radiofrequency (RF) electromagnetic waves was demonstrated by many phase III trials for several tumor sites when combined with ionizing radiation [5] and a number of chemotherapeutics [6–9]. Of relevance, no increase in late toxicity induced by HT was found in these studies, making heat a potent enhancer of current cancer treatments without adding to their long-term side effects. Although clinical work to date has demonstrated only temperature dose-effect relations [10], biological work also showed the impact of heat-mediated perfusion modulation on therapy outcome [11]. In addition, HT is being studied for enhanced local drug delivery by heat-mediated release of drugs encapsulated in thermosensitive liposomes [12,13]. These are important incentives to combine HT with chemotherapy, especially via controlled localized heating that can be achieved with electromagnetic-based methods such as radiofrequency (RF) and microwave (MW). Recent developments in RF/MW HT device technology are enabling significantly more localized application of HT, but a detailed review is currently not available.

This review summarizes the current clinical status, recent developments and potential of RF and MW induced heating aimed at its utility in local drug delivery. It first reviews the basic principles, strengths and limitations of RF and MW, continues with all clinical studies per anatomical site involving RF/MW HT as adjuvant for chemotherapy, reviews the potential of new RF/MW technologies entering the clinic and finalizes with a future outlook. The review is kept broad as to enable comprehensive assessment of the field by medical doctors, basic researchers, physicists, and engineers. Further, it is designed for both newcomers in the field as well as more established researchers and clinical personnel.

2. Physics of radiofrequency and microwave mediated hyperthermia

2.1. Aim of hyperthermia

The goal of HT is to raise temperature in tumors to render the cells more sensitive to ionizing radiation and chemotherapy [14,15]. The proven effectiveness of HT relies on its thermal effect on tumors that is dependent on both temperature and heating time, as shown by preclinical [16–18] and clinical studies [19–23]. The sensitization occurs mostly via increased blood perfusion, increased oxygenation, inhibition of radiation-induced DNA damage repair, and boosting local/systemic immune response [24].

The range of the therapeutic temperature goal in tumors differs in literature and treatment protocols by a few degrees centigrade, but span within 39–45 °C [5]. The difference is explained with evolving knowledge of HT effects, but also depends on the type of combination with other therapeutic agents and location in the body. The suggestion of an expert panel at ESHO 2018[1] defined the goal temperatures to be 40–44 °C, which has now been widely accepted. This temperature range is nevertheless based on a strong evidence coming from clinical studies that combines HT with radiotherapy and can be slightly lower for the protocols combining HT with chemotherapy, i.e., 39–43 °C [5]. This range is related to increases in perfusion found at 39 °C and the finding that temperatures greater than 43 °C increase the risk for vascular damage [25], which will reduce the amount of drug that can be delivered to the tumor. It should be emphasized that a benefit of HT has been clinically demonstrated only when applied in combination with chemotherapy and/or radiotherapy [5,6]. In current practice, HT is applied for 60 min before/after radiotherapy within a 0.5–4 h window, while with chemotherapy, HT is applied simultaneously or shortly after the chemotherapeutic regimen [14]. Section 3 of this review provides an in-depth analysis of the clinical trials to date involving heat and chemotherapy.

2.2. Heating by RF and mw

Many different electromagnetic (EM)-based technologies have been used to apply HT. Their main difference is the applicator frequency: 3 Hz to 300 MHz (RF), 300 MHz to 300 GHz (MW), and 300 GHz–430 THz (infrared, IR). This chapter will cover the RF/MW devices and their use in clinical trials, where the transition from RF to MW is defined to be at 300 MHz.

When applying RF/MW energy in the human body, all tissues behave as lossy dielectrics, i.e., they are both poor insulators and poor electrical conductors. The tissue heating mechanism varies with frequency of the EM wave. At RF below approximately 30 MHz a process known as joule heating occurs as a result of ion movement due to applied EM field, causing energy dissipation by friction and collision with surrounding molecules, leading to local heating of tissue.

The radiative mode of EM propagation and dielectric losses in tissue come into being predominant at frequencies above 100 MHz. Heating is generated primarily by mechanical frictions between adjacent polar water molecules, which oscillate 100 million cycles per second in the time varying electric field.

The interaction of RF/MW fields with biological tissue is typically investigated using a macroscopic model including the dielectric properties: effective electrical conductivity σ (units of S/m) and relative permittivity ε_r (unitless). The effective electrical conductivity embodies all electrical losses in the material due to the currents driven by the EM field. The relative permittivity describes the ability to polarize a material subjected to an applied EM field. Both properties are tissue, frequency and temperature dependent [26–28] and can be modeled mathematically using empirical data [29,30]. An overview of normal human dielectric properties was originally measured and tabulated by Gabriel et al. [30]. A more comprehensive database

[1] 32nd Annual Meeting of the European Society for Hyperthermic Oncology, Berlin, Germany May 16–19, 2018.

that also includes thermal and physiological properties is accessible in the IT'IS Tissue Properties Database [31].

The EM energy is converted into heat through the lossy nature of the tissue. The energy absorbed in tissue is often described by the Specific Absorption Rate (SAR) with units of W/kg. The SAR parameter corresponds to the rate at which EM energy is absorbed per unit weight of tissue, and can be calculated using either of the two equations:

$$SAR = \frac{\sigma |E|^2}{2\rho} \quad (1)$$

$$SAR = C_p \frac{dT}{dt} \quad (2)$$

where ρ is the mass density (kg/m^3), E is the magnitude of the local electric field (V/m), C_p is the specific heat capacity (J/kg/°C) of the tissue and dT/dt is the initial heating rate (°C/s). The right-hand side of Eq. 2 suggests the relation of SAR and initial temperature rise in tissue when thermal conduction and thermal convection effects are neglected. As an example, to increase the temperature of muscle tissue by 1 °C in 1 min, an average SAR of 60 W/kg is required [32]. To model a heat transport in the human body in the treatment planning phase, the Pennes bioheat transfer equation is commonly applied [33]. However, neither heat exchange between tissue and realistic vasculature, or for the direction of blood flow is accounted in this straightforward model. The most accurate calculations are thus performed by modelling of the vasculature discretely, also known as a discrete vasculature (DIVA) model [34]. At the moment, the main hurdle for DIVA modelling is the inability to discriminate vessels down to the required 0.1 mm diameter using current imaging modalities in a clinically realistic time [35,36]. Hence, currently the PBHE is mostly used due to its simplicity and validity in tissues with small (< 0.1 mm in diameter) blood vessels.

In order to quantify the hyperthermic effect reported in different studies and to assure treatment reproducibility, a relationship between thermal exposure and thermal damage has been defined. In a proposed thermal-dose relationship, often referred to as thermal isoeffect dose (TID) or cumulative equivalent minutes at 43 °C (CEM43) [15,37,38], it was shown that for every 1 °C rise in temperature above 43 °C, cell killing doubles while cell killing diminishes by about one quarter for every 1 °C below 43C. In order to reflect the limited information about the spatial and time distribution of the achieved temperatures in treated area as provided by the current thermometry, a treatment descriptor has been modified to consider the 10th percentile of the temperature distribution (T90). The current expression CEM43T90 thus compares different tissues in terms of their thermal-dose sensitivity is a combination of CEM43 with a threshold temperature T90. An alternative thermal dose parameter is TRISE, which is based on the temperature exceeded by 50% of measurement points and duration of heating [22]. All the above parameters display some conceptual weaknesses as they represent the effect of the entire history of heat exposure on cell death, but they do not include the radio- or chemo-sensitization effect [10]. Nonetheless, there is a strong correlation between thermal dose and clinical outcomes as has been shown by several clinical studies [23,39–41]. Thus, in order to achieve optimal therapeutic results, adequate temperature must be delivered for an appropriate period of time to the entire tumor volume. Therefore, and despite some limitations in capturing the full hyperthermic effect, CEM43 and TRISE have been identified as two of the most important measures of the treatment efficacy when combining radiation with HT to treat cancer [10]. This correlative effect is expected, but not yet validated, in thermochemotherapy treatments. Details about the thermal dose concept are given in the reference [42] of this issue.

2.3. Different techniques to induce localized heating

A summary of different techniques to apply HT is given in Table 1 and is complemented by Table 2, which lists all HT applicators that are commercially available and have been used in clinical thermochemotherapy trials.

2.3.1. Superficial hyperthermia

Localized heating of superficial tumors has been the largest clinical application of HT to date, owing to the accessibility for heating devices, thermometry and clinical observation. However, it has been used prevalently in protocols that combine HT with RT.

In general, superficial heating devices apply energy to heat a limited volume of tissue close to the heating device. Power deposition decreases exponentially as radio/microwaves penetrate through tissue. In general, higher MW frequencies provide localized heating of skin and superficial tissues, while the lower frequencies will heat larger and deeper regions in the body. The penetration depth from the skin surface, often defined in HT as half-power depth, is 10 cm at around 10 MHz. Superficial heating within 2–4 cm from the skin can be obtained by applying frequencies in the range of 400–1000 MHz.

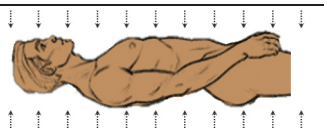
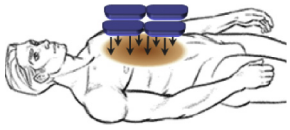
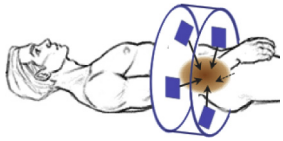
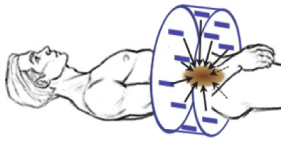
The EM energy is directed to the treated volume by applicators placed on the surface with a water bolus, which provides EM coupling between the applicator and the body. The water in the bolus is circulated at a controlled temperature [45,46], thus protecting the skin from potential burns. Based on the MW frequency, often 434 or 915 MHz, the typical thermal penetration depth is 3 cm but can be increased to a maximum of 4 cm (at 434 MHz) by lowering the water bolus temperature [46]. Furthermore, it is important to be aware that large applicators achieve better penetration depth than small applicators operating at the same frequency. Covering of large tumors by desired thermal dose can be achieved by combining of several applicators into multi-element arrays where power output of each element can be controlled independently. As suggested in Table 2, EM applicators can be categorized in three classes: waveguide, microstrip, and electrode-based applicators. A more in-depth overview of the operating principles, strengths and weaknesses of superficial heating systems is given in [47], while more detailed description is provided by several reviews [48–50] and a dosimetric analysis for radiative and capacitive is given in [51].

2.3.2. Deep hyperthermia - external heating

An effective HT treatment aims to concentrate heat in the tumor area, while sparing surrounding healthy tissue from temperatures of 43–45 °C [52,53]. Beyond approximately 2 cm from the skin, the temperature goal is often better achieved with a phased-array approach, where an array of antennas is placed around the patient. The antennas are then suitably fed in amplitude and phase to create a constructive wave interference to selectively heat the target region. For all EM waves, a circumferential array is the optimum arrangement since this maximizes the interference of the transverse waves, i.e. with the electric field component of the EM wave oriented along the patient-axis (Fig. 1). The steering parameters of phased-arrays include the amplitude, 0phase and frequency of the antennas, which are optimized during treatment planning as discussed in section 4 and reviewed in references [54, 55].

The operating frequency is a critical parameter in a phased-array system. At first, it determines the penetration depth that is achievable with a certain system. Second, it also determines the size of the temperature focal spot, which is approximately one half of the wavelength. For the practical range of frequencies used in HT, the wavelengths in soft tissue vary from about 4.5 cm at 1000 MHz up to 2 *m* at the lower 1 MHz frequencies. The spatial resolution of higher frequencies can be achieved by increasing the number of antennas within the applicator, which

Table 1
Summary of electromagnetic-based hyperthermia techniques for cancer treatment.

Heating approach		Heating region	Typical frequency (f) & number of Antennas	Typical therapeutic heat focus (region at 40–44 °C)	
External	Whole body	Regional	f = 200–375 GHz	Whole body (38.5–40.5 °C for >3 h or 40.5–42 °C for1–2 h [43,44])	
	Superficial	Local (near the surface)	f = 400–1000 MHz one applicator (single or multi-antenna)	Block-shaped: footprint typically 10 × 10 cm^2 Volume: 200–400 cm^3	
			f = 400–1000 MHz Combination of multiple applicators	Block-shaped: footprint typically 20 × 30 cm^2; Volume: 120S0–2400 cm^3	
	Deep	Regional	f ≤ 100 MHz 4 antennas/channels *Heat focus steering in radial direction*	Ellipsoidal shape: 15–20 cm in the main (patient) axis Volume:1750–4000 cm^3	
		Locoregional	f = 100–300 MHz, 4–12 antennas/channels *Heat focus steering in radial and axial direction*	Ellipsoidal shape: 8–15 cm in the main (patient) axis Volume: 250–1750 cm^3	
		Local	f = 300–1000 MHz 12 ≤ antennas/channels *Heat focus steering in radial and axial direction*	Ellipsoidal shape: 1.5–8 cm in the main (patient) axis Volume: 15–250 cm^3	
Internal	Interstitial (deep)	Local	f = 27, 434, 915 MHz 3–16 antennas/channels	Volume: 30–120 cm^3	
	Intracavitary/Intraluminal (deep)	Local	f = 27, 434, 915 MHz 1 antenna	Volume: 5–30 cm^3 *in case of bladder cancer, the complete 400-600 ml volume*	

counteracts the lower penetration depth. Increasing the number of antennas further improves both penetration depth and the steering capabilities of the applicator. As shown in Table 2, the most common applicator is a phased-array system based on dipole or waveguide antennas. However, smaller alternatives such as the patch [56–58] or bow-tie [59,60] antennas are being utilized in yet uncommercialized devices.

Another approach to achieve heating at depth is to utilize capacitive systems. In this approach, the patient is positioned on a treatment bed with an embedded electrode while another electrode is placed on the patient. The electrodes connected to a high-power RF generator working at frequencies 8–40 MHz [61]. The heating pattern can be modulated installing electrodes with different dimensions, where the heating will be concentrated near the smaller electrode by concentrating the electric currents. When applying RF-capacitive heating, an important factor to consider is unintentional preferential heating of subcutaneous fat. Dedicated vigorous cooling strategies are being applied to enable heating beyond the fat [62].

The first, pioneering studies in semi-deep regions were performed with capacitive systems as those were believed the only ones to deliver effective proportion of energy in depth, were affordable and rather straightforward to use. The introduction of smaller antennas serving as applicator elements along with advances in treatment planning led to increased use of radiative systems, especially in Western countries. A number of simulation studies that studied differences in heating characteristics between capacitive and radiative systems and effect of these differences on heating quality has been recently performed and published [51,63]. A representative temperature distributions achieved with the two distinct techniques are shown in Fig. 2.

2.3.3. Deep hyperthermia – internal heating

Internal heating can be achieved via interstitial, intraluminal or intracavitary RF/MW applicators, which apply energy within a limited volume of tissue close to the heating device(s). Interstitial HT is often used in combination with brachytherapy; it uses a needle-shaped antenna/electrode that is either implanted directly in tissue or inserted in catheters that are implanted into the target volume. Due to steep radial fall-off of energy is heating limited to radius of 5–10 mm from the applicator. Interstitial heating thus requires use of multiple applicators. Intraluminal and intracavitary techniques utilize the same heating concepts, but applicators are placed within tubular organs like esophagus and urethra (intraluminal) or natural body cavities like bladder or cervix (intracavitary). There is a high variety in applicator designs, ranging from MW antennas, capacitively-coupled RF catheter-based electrodes, resistively-coupled RF local current field electrodes, ultrasound systems, as well as hot source techniques. A more in-depth overview of operating principles of

Table 2
List of MW/RF commercial medical devices used in clinical trials that combined adjuvant hyperthermia with chemotherapy. The references listed are the ones that best explain the physical principles of each MW/RF device.

	Device	Manufacturer, country	Applicator	Array description	HT delivery	Frequency (MHz)	Monitoring	References
Radiative	Alba 4D	Medlogix, IT	Alba 4D	1 ring with 4 waveguide antennas	External Deep Locoregional	70	4 or 8 thermocouple multi-sensors (56 sensors total) 1 optical *E*-field sensor	[88]
	Alba ON4000		Alfa, Beta, Gamma, Delta	1 or 2 contact curved microstrip antennas	External Superficial Local	434	8–32 thermocouples, 1 blood perfusion doppler	[89]
	BSD-500	Pyrexar Medical, US	MA-151, MA-100, MA-120	1 rectangular waveguide	External Superficial Local	915	8 thermistors	[49]
			SA-308, SA-510, SA-812, SA-248	3, 5, 8, or 24 Archimedean spiral antennas				[90]
			MA-251	1–24 dipole antenna wires driven by 8 channels	Interstitial Deep Local			[91]
	BSD-2000		Σ-30, Σ-60, Σ-Ellipse	1 ring with 4 dipole antenna pairs	External Deep Regional	75–140	8 thermistors, thermal mapping	[92]
			SA-115	1 Archimedean spiral antenna	External Superficial Local	98–140		[93]
	BSD-2000 3D		Σ-Eye	3 rings with 4 dipole antenna pairs per ring	External Deep Locoregional	100	8 thermistors, thermal mapping	[94]
	BSD-2000 3D/MR		Σ-30-MR, Σ-Eye-MR	1 or 3 rings with 4 dipole antenna pairs per ring	External Deep Locoregional	100	8 thermistors, thermal mapping, MR guidance	[95]
	Synergo® RITE	Medical Enterprises, NL	SB-TS 101	1 half wavelength not centrally fed skirt type antenna	Intracavitary Deep Local	915	3 thermocouples	[96]
	Yacht-3	JSC MC SEZ Istok, Fryazino, RU	4 rectangular applicators 1 circular models		External Superficial Local	915	Up to 18	N/A
			3 circular models		Intracavitary Deep Local			
	Yacht-4		5 rectangular applicators		External Superficial Local	434		
			3 circular models		Intracavitary Deep Local			
Capacitive	Oncotherm	Oncotherm Kft., HU	EHY-1020 IL	Mobile electrode + stationary counter-electrode	Intracavitary Deep Local	13.56	No monitoring available	[97]
			EHY-2030 EHY-2000+		External Deep Regional			
	Thermotron	Yamamoto Vinita Co., Ltd., JP	RF8	1 pair of circular electrodes	External Deep Regional	8	5 thermocouples	[61]
	HY7000	Nanjing Greathope Co., Nanjing, CN	HY7000	2 pairs of perpendicular electrodes	External Deep Regional	40.68	Superficial readings only	[98]
	Incoherent Dual RF Hyperthermia System	Morestep Science & Technology Development Co., Ltd., Changchun, CN	NRL-001	2 pairs of perpendicular electrodes	External Deep Regional	30.32 or 40.68	Undefined number of thermocouples	[99]

internal heating techniques can be found in [64–66] while a list of clinical devices and their comparison is given in [67].

2.3.4. Applicator selection

Due to the strong correlation between applied thermal dose and therapeutic outcome, adequate temperature must be delivered for an appropriate period of time (approximately 60 min) to the entire tumor volume. Therefore, heating devices must be technically capable to deliver the required/planned thermal dose into the specified target volume, while minimizing heating of the surrounding healthy tissues. Based on the specific target volume and location, an appropriate heating technique from Table 1 in combination with the listed critical points can be selected as the first step to plan a treatment. Nevertheless, various RF/MW systems have unique characteristics, benefits and limitations that need to be further considered. The recent ESHO Quality Assurance

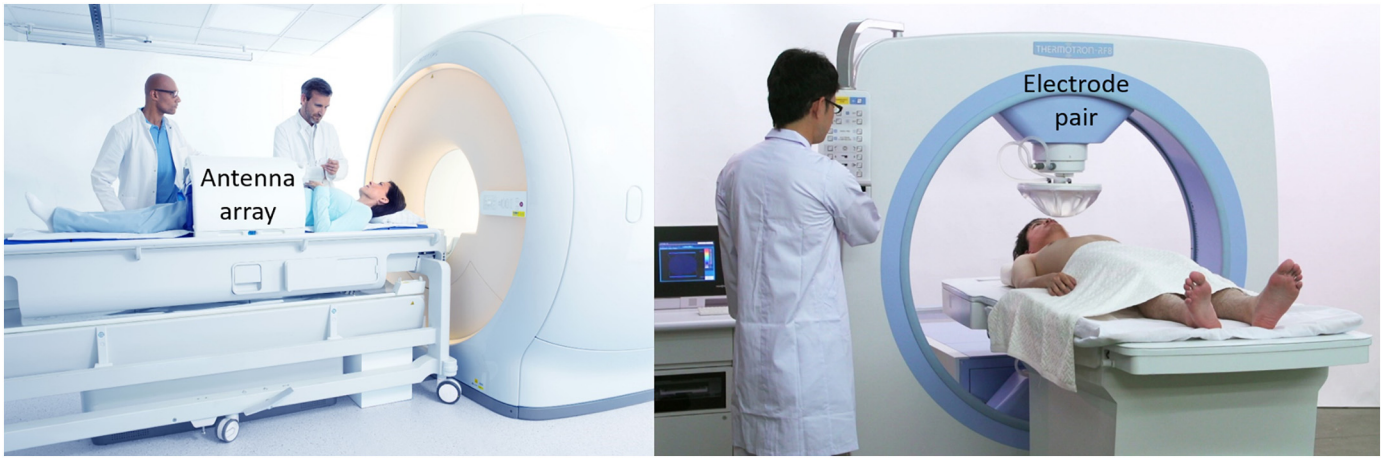


Fig. 1. Example of two RF hyperthermia systems: radiative-based BSD-2000 3D/MR courtesy of Pyrexar Medical, USA (left); and capacitive-based Thermotron RF-8EX courtesy of Yamamoto Vinita, Japan.

guidelines for superficial, interstitial and deep HT [47,67–69] can further help the user to identify clinical conditions where a particular heating device can be used. Critical points for applicator selection are:

1) Tumor depth below the tissue surface – Due to exponential decrease of power deposition, the applicator selection is strongly dependent on the tumor depth. For tumors located deeper than 3–4 cm, phased-array applicators should be used but the penetration depth of the radio/microwaves determines the selection of the working frequency even in this situation. The frequencies applied clinically are in the range 70 to 140 MHz for tumors located in the pelvic region [70], and 434 MHz for head and neck region [71]. Devices using internal RF/MW sources can be used if suitable. Treatment planning tools can be valuable to find the most appropriate technique [72].
2) Tumor size – The applicator must be capable to heat the entire target volume. In case of superficial applicators, an applicator with thermal effective field size (TEFS) that covers the complete target volume should be used. The size of TEFS is often limited by the footprint of the aperture. In case of phased arrays, the operational frequency influences the special resolution of power deposition and should be carefully chosen. In case that the applicator cannot cover the whole target volume, multiple abutting fields should be outlined to cover the target entirely, and then administered sequentially.
3) Proximity to adjacent critical normal tissue structures – HT treatment planning is recommended in cases where the tumor is adjacent to critical tissues or adjacent to metallic/breast implants. Implants are not cooled with blood perfusion and metallic implants concentrate electric currents, potentially giving rise to unwanted local hot spots that can be treatment-limiting. Treatment planning

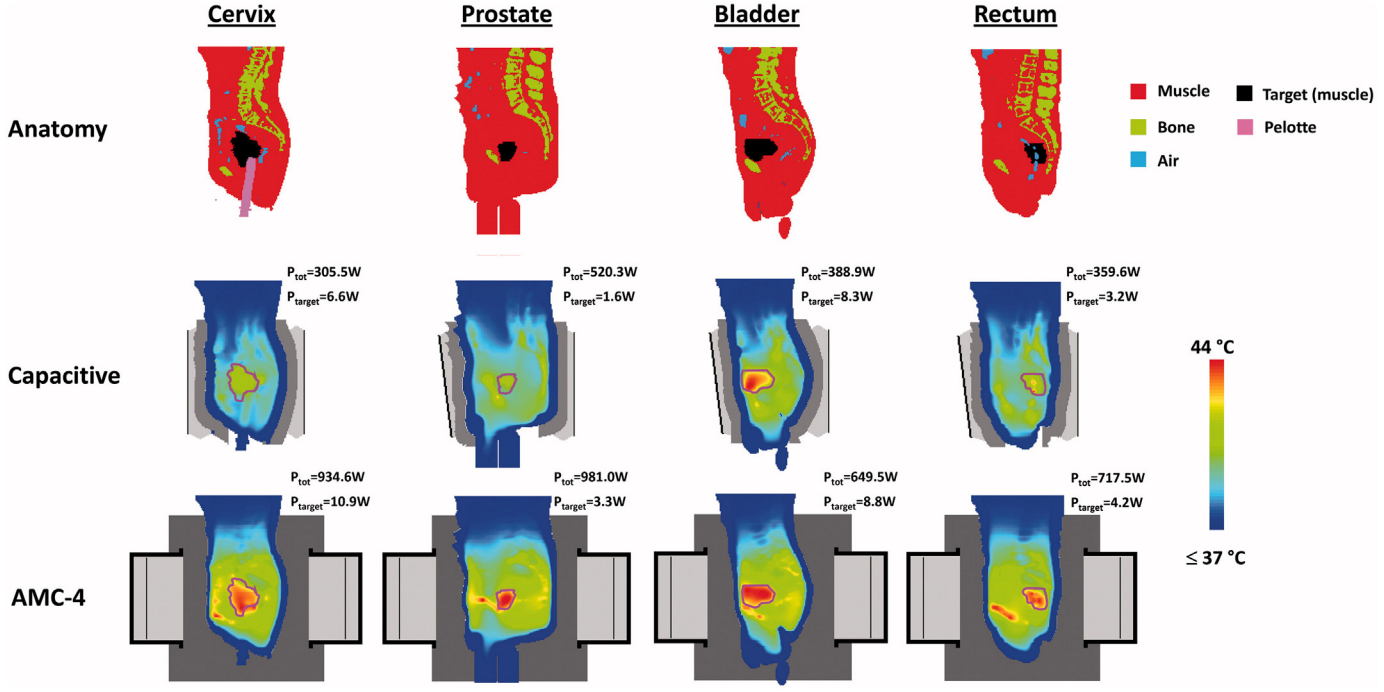


Fig. 2. Sagittal slices of simulated temperature distributions for patients with fat layer <2 cm with cancers in different sites (cervix, prostate, bladder and rectum) heated with 13.56 MHz capacitive electrodes and with conventional 70 MHz radiative device (AMC-4). The maximum temperature in all distributions is 44 °C. The total power absorbed in the patient (P_{tot}) and in the target region (P_{target}) is indicated for each distribution. Slices were taken approximately through the center of the patient. The contour in the temperature distributions indicates the target region. Reprinted from open access reference [63].

is also recommended for superficial and intracavitary/interstitial HT [73]. When applying RF-capacitive heating, caution must be taken to prevent unintended heating of the fat tissue layer. In deep HT, the adaptive optimization algorithms that have been developed in recent years are powerful tool to achieve high tumor temperatures even in challenging cases [54,55].

2.3.5. Comparison to other techniques

Applicators based on RF/MW technology are currently the most commonly used when treating cancer patients with HT. During the last few years there has been a growing interest for using ultrasound (US) to induce HT, due to its higher penetration depth and mm-scale focusing capabilities [74]. Initially developed to thermally ablate (>55 °C) small tumors [75,76], focused ultrasound (FUS) can ablate up to ~16 mm tumors by focus steering, and larger tumors by sequentially ablating the whole volume. FUS for mild-to-moderate temperatures of 40–44 °C, i.e. HT, has been proven promising in small animal tumors (<1.3cm^3) [76–78], but application in humans is still undergoing clinical trials [79–81]. Compared to US, RF/MW techniques have the highest potential to cover and treat tumors larger than 4 cm and in regions near the skin, bone structures or air cavities. A more detailed coverage of the potential for FUS hyperthermia can be found in [81].

2.4. Treatment monitoring

Thermal dose monitoring is a critical instance of the HT treatment that enables to control and evaluate in real-time the quality of the treatment. The invasive measurements in tumor-related reference points are still regarded by many clinicians as a gold standard. Multiple sensors are either placed to measure temperatures across the treated area, or cyclically pulled through catheters to map temperatures in invasively placed catheters or across the skin surface (thermal mapping). Stationary probes are typically used as references for real-time feedback power control to maintain temperatures in the target between 40.0 and 42 °C for 30–60 min, as is optimal for enhancing perfusion as well as thermal sensitization, and simultaneously below 44.0 °C in healthy tissues to avoid overheating. Often, manual intervention by the operator is needed to trigger adjusting the power to keep temperatures within the desired range. Techniques that are used to assess temperatures during HT treatment include thermistors, fiber-optic probes and thermocouples [69,82].

Unfortunately, invasive thermometry approaches typically involve the use of only a few monitoring positions, which often result in under sampling of temperatures in areas with significant temperature gradients [83]. Moreover, the insertion of intratumoral thermometers may restrict the number of patients being treated with HT due to potential complications associated with the invasive procedure. The recent trend in thermal dosimetry for deep-seated and regional HT is the use of non-invasive techniques based on MR. However at this moment this approach is not standard in the clinic and clinical trials on RF/MW hyperthermia. Non-invasive techniques based on MR are described in detail in chapter 4.

Besides temperature, other relevant clinical parameters to be monitored include blood flow (units L/min) and blood perfusion rate (units kg/s/m^3 or mL/min/kg), where the latter reflects the blood perfusion in the microcirculation bed. Note that in response to heating, blood perfusion is upregulated by the body to reduce tissue temperature back to the homeostatic set-point. Real-time measurement of the temperature and/or perfusion enables to adjust the applied power to maintain the desired temperature elevation. Chemotherapy benefits from HT due to increased blood perfusion in tumors that is accommodated with increased permeability of the tumor blood vessels, thus improving the leakage of drugs where heating is occurring [84]. Monitoring blood perfusion and/or blood flow can be estimated based on dedicated measurements with invasive thermometry [85] but is currently commercially only available for the Alba ON4000 superficial unit (Table 2) using doppler techniques. Another approach to monitor blood perfusion is to use contrast enhanced (DCE) magnetic resonance imaging (MRI), which has been used to predict response of locally advanced breast cancer patients to neoadjuvant chemotherapy and HT [86]. The contrast of DCE-MRI distorts MR thermometry and good signal-to-noise imaging is required, which is not readily available for EM applicators.

Finally, hyperthermia treatments are generally conducted without anesthesia or sedation. This is critical for two reasons: 1) patients can provide feedback about pain induced by hot spots, thus improving safety profile of the treatment; and 2) anesthesia impairs normal thermoregulatory function (see e.g. [87]), which limits the ability to increase blood perfusion as a response to higher therapeutic temperatures. The exceptions are for whole body hyperthermia, which is conducted with deep sedation or general anesthesia [43], and for hyperthermia treatments in children, where mild to deeper sedation is provided to reduce anxiety and restlessness [8].

3. Clinical applications of RF and MW mediated hyperthermia

HT has been successfully used in combination with radiation therapies since the 70s. The pioneering work on cervical [100], breast [101], head and neck cancer [102] has defined the basis for present protocols and acceptance of hyperthermia. The most recent overview of randomized trials and metanalyses combining hyperthermia with radiation is given in references [5,103]. Following a similar trend, adjuvant HT has rapidly expanded its use to increase local drug delivery and local cytotoxicity of systemically administered chemotherapeutic agents. A comprehensive summary of trials primarily combining hyperthermia with chemotherapy is however currently missing. Thus, this section summarizes the clinical trials that studied the effect of HT as adjuvant to chemotherapy (CT), or chemoradiation (CRT) if chemo-stimulation was the goal, i.e., chemotherapy plus HT (CHT) and chemoradiation plus HT (RCHT). In this section, we only included those trials where HT was delivered with RF/MW devices. The commercially available devices used in these clinical trials are listed in Table 2, while details about other devices no longer available are given as a footnote.

3.1. Bladder cancer

Colombo et al. conducted a multi-center randomized trial comparing the use of mitomycin C alone and in combination with the Synergo intracavitary MW device for the treatment of non-muscle invasive bladder cancer [104]. At 2-year follow-up, 83 patients were accrued and the recurrence-free survival in the combined arm was significantly higher: 82.9% (CHT) vs. 42.5% (CT). The long-term outcomes were reported in 2011: 10-year disease-free survival (DFS) was 52.8% for CHT vs. 14.6% for CT; and bladder preservation rates were 86% for CHT and 79% for CT [7]. The use of regional HT with intravesical mitomycin C was analyzed in a pilot study ($n = 18$) with the external AMC 70 MHz device using 1 or 2 rings of four waveguide antennas per ring. This device was the precursor of the commercially available Alba 4D. The recurrent-free survival was 78% at 24 months without any grade 3 or higher toxicities [105]. Another pilot study ($n = 45$) analyzed the combination of regional HT (BSD-2000 3D), radiation and chemotherapy (cisplatin, 5-fluorouracil, carboplatin, or paclitaxel) to treat high-risk T1 and T2 bladder cancer [106]. Grade 3 and 4 sequelae were reported in 24% of the patients, but overall survival (80%) and bladder-preserving rate (96%) at 3 years follow up were quite encouraging.

3.2. Sarcomas

In 2010, Issels et al. reported a phase III multi-center European Organization of Research and Treatment of Cancer (EORTC) trial in localized high-risk-soft-tissue sarcoma. This was a large trial with 341 patients randomized to receive a three-drug-regimen alone or with regional HT using BSD-2000 equipment [107]. Treatment response was significantly improved in the CHT group with 28.8% responders compared to

12.7% for the CT regimen alone. A recent follow-up of this trial reported prolonged survival rates in CHT when compared with CT alone: 10-year survival of 52.6% vs 42.7% [6]. The results indicate that regional HT from an RF array applicator combined with the three-drug-regimen can be given safely with moderate and acceptable toxicity, accompanied by significantly improved clinical response. Another clinical trial studied the multimodality RCHT treatment using the Thermotron RF-8 device combined with cisplatin and pinorubin as drugs [108]. Tumor shrinkage was observed in 43 out of 44 patients (98%) and there was recurrence in only one patient. Of the 36 patients who presented M0 tumors (i.e., no disease in distant sites), 30 were disease-free at final follow-up and 2 had no evidence of disease.

3.3. Head and neck cancer

Three randomized trials studied the effects of tri-modality RCHT vs. conventional RCT for treating nasopharyngeal carcinoma [109–111]. Hua et al. used cisplatin +5-fluorouracil with an intracavitary 915 MHz device,[2] Kang et al. used cisplatin only with external 915 MHz radiators,[3] and Zhao used cisplatin + paclitaxel with external RF capacitive 13.56 MHz HT.[4] All studies showed significantly improved outcomes with added RF/MW HT. Local control rates increased from 12.2% (RCT) to 19.2% (RCHT); 5-year survival increased from 7.9% to 18.4% with HT; 5-year progression-free survival increased 9.6% [109]; 5-year DFS increased 30.8% [110]; and average DFS increased from 37.5 to 78 months [111]. Two of these studies evaluated complete response (CR), reporting that the addition of HT increased CR from 81.1% to 98.6% in one study [109] and from 62.8% to 81.6% in the other [110]. Quality of life (QoL) was assessed by Zhao et al. and patients that received HT showed significantly improved QoL scores [111]. Furthermore, Datta et al. performed a systematic review and meta-analysis of RT + HT in the management of head and neck cancers using RF/MW devices [102]. Although the role of CT was not included, the authors highlighted that various phase I/II trials and preclinical studies have shown that a tri-modality therapy adding cisplatin with HT + RT can achieve a synergistic effect that can translate into clinical efficacy.

3.4. Esophageal cancer

Three randomized studies demonstrated an advantage in the treatment of esophageal cancer when adding HT to CT or RCT [112–114]. In one of these studies, 53 patients were treated with HT using the intraluminal Endoradiotherm 100A device[5] (13.56 MHz internal electrode + external planar electrode) and histopathologic response was significantly improved in the tri-modality arm: 66.7% vs. 38.5% [112]. In addition, 70.4% of patients treated with RCHT stated an improvement in swallowing capability, while only 7.7% of patients reported improvement in the RCT group. In a follow-up study [113], an additional 40 patients were randomized between CT and CHT yielding a favorable histopathologic response for the dual-modality CHT treatment (41.2%) vs. CT alone (18.8%). A third randomized trial used an intraluminal 915 MHz microwave applicator (model undisclosed) for heating, which reported a 3-year survival rate of 42.4% in the RHT group vs. 24.2% for RT alone [114]. Kuwano et al. conducted the largest clinical trial to date ($n = 243$) studying the effects of intraluminal RF HT combined with chemotherapy and irradiation on esophageal cancer overall survival (OS) [115]. Both pathological CR (8.4% vs. 19.1%) and 5-year OS (13.7% vs. 22.3%) where significantly higher in the RCHT group, when compared with the standard of care. More recent single-arm studies of adjuvant heat have further validated extended survival in esophageal cancer patients with 5-year OS of 50.0% (n = 24) [116] and 3-year OS of 42.5% ($n = 50$) [117]. Toxicities were reported to be tolerable and limited to grade 2 or 3 in all studies. Nakajima et al. [116] used the Endoradiotherm 100A device and Sheng et al. [117] used a RF capacitive heating device based on a spiral strip applicator design (unknown frequency).[6]

3.5. Rectal cancer

In a retrospective study of 106 patients treated with 5-fluorouracil and radiation with/without hyperthermia (BSD-2000 system), the pathological CR (pCR) in the RCT group was seen only in 6.7% of patients, whereas in the RCHT group a pCR of 16.4% was achieved [118]. These results were even more impressive when analyzing the subset of patients that received four or more HT treatments, who presented a significantly higher pathological CR of 22.5%. Despite these encouraging results in terms of pCR, translation to improved local control and/or overall survival still needs to be determined. In a retrospective trial of neoadjuvant RCT with regional HT using the BSD-2000 system, Maluta et al. observed a local control rate of 100% at 5-year follow-up for all patients who achieved pSCR (18 of 76) [119]. In two more recent phase II trials, the use of capecitabine, radiation and capacitive HT was analyzed yielding impressive results. Barsukov et al. accrued 64 patients and used an RF capacitive 14 MHz device,[7] adding oxaliplatin and metronidazole to a capecitabine regimen: the 2-year OS and DFS was 91% and 83%, respectively [120]. Using only capecitabine and an intracavitary 433 MHz Yachta-4 device, Rasulov et al. achieved in 81 patients a 97% 3-year OS and 85% 2-year DFS regimen [121] in a single arm study.

3.6. Anal cancer

The clinical benefit of adding intracavitary HT (customized 433 MHz dipole antenna) to a RCT regimen was explored in a randomized trial in anal cancer patients [122]. After a 5-year follow up, 68.0% of the patients in the CT arm had sphincter preservation, whereas 95.8% of the patients in the RCHT arm preserved their anorectal function and avoided permanent colostomy. In the HT arm, locoregional recurrence was significantly higher (32.0% vs 4.2%), and the local recurrence-free survival time was also significantly higher (59.7% vs 50.4%). A more recent non-randomized trial compared RCT with and without deep regional HT (BSD-2000 3D and BSD-2000 3D/MR) in patients with anal cancer [123]. The chemo regimen included 5-fluorouracil and mitomycin C. After 5 years follow-up, disease-free (89.1 vs. 70.4%), local recurrence-free (97.7 vs. 78.7%), colostomy-free (87.7 vs. 69.0%), and overall survival rates (95.8 vs. 74.5%) were significantly better for the RCHT group. Grades 3–4 toxicities were comparable except for hematotoxicity (66 vs. 43%) and telangiectasia (38.0 vs. 16.1%) that were higher in the RCHT group.

3.7. Lung cancer

Shen et al. randomized 80 patients to gemcitabine and cisplatin with and without heat administrated by the capacitive RF regional heating using the HY7000 device [124] for the treatment of non-small cell lung cancer (NSCLC). Although there was no significant difference in response rates, the clinical benefit response (a clinical index used with incurable tumors to assess improvement in quality of life) was significantly higher in the CHT group: 82.5% versus 47.5%. Using the same trial modality and heating device, Yang et al. evaluated retrospectively the medical records of 93 patients with advanced NSCLC [98], where the overall response rate of pleural effusions was significantly better in the CHT (81.2%) group than in the CT group (40.0%). The patients in the CHT group also presented lower incidence rate of weakness

[2] WE2102-A MW hyperthermia system, Yuan De Biomedical Engineering, Beijing
[3] Pingliang 778WR-L-4 MW hyperthermia machine, Sunostick Medical Technology Co., Ltd., London, UK
[4] HG-2000-type RF applicator, Zhuhai Hokai Medical Instruments, Guangzhou, China
[5] Endoradiotherm 100A, Olympus Optical Co. Ltd., Japan
[6] HRL-001, Jilin Maida, China
[7] Yagel, JSC MC SEZ Istok, Fryazino, Russia

(12.5% vs. 46.7%) and gastrointestinal adverse reactions (25.0% vs. 77.8%) than in the CT group. No significant differences were shown in the objective tumor response and survival rates. Wang et al. [125] performed a clinical study with the NRL-001 RF regional heating device using the same drugs (gemcitabine and cisplatin) in 119 patients with advanced NSCLC, but adding a third treatment arm with radiation. A remarkable curative rate was achieved with tri-modality treatment: 90.7% (RCHT) vs. 72.8% (RCT) and 62.2% (RT). Although toxicity increased in the RCHT group, it was reported to be tolerable or readily alleviated with short-term symptomatic treatment. Overall, patients treated in the tri-modality arm achieved significant higher quality of life and improvement in alleviation of tumor oppression syndrome.

3.8. Other cancers

Datta et al. performed a network meta-analysis (NMA) of four different treatment regimens for cervical cancer: RT, RHT, RCT, and RCHT [126]. The pairwise comparison of various groups showed that RCHT was the best option for both CR and patient survival. A wide range of RF/MW heating devices were used for these studies including regional heating with either capacitive or radiative RF systems or intracavitary heating with custom-built coaxial applicators. In 1984, the use of 2.45 GHz local irradiation using an intracavitary device was explored in combination with a bleomycin + mitomycin C regimen to treat vaginal cancer. The positive response rate increased to 59.5% compared with 19.2% when using CT alone. Two pilot studies explored the use of thermally enhanced drug delivery using low temperature liposomal doxorubicin in heavily pretreated patients with chest wall recurrences [13]. Heating was achieved with BSD-500 equipment that uses multiple microwave applicators that heat up to 3 cm deep. These trials demonstrated safety and objective responses in heavily pretreated patients with chest wall recurrence. A recent systematic review compared 14 phase I/II clinical studies ($n = 395$) on locally advanced and/or metastatic pancreatic cancer patients that used adjuvant HT [127]. Patients were treated with regional capacitive/radiative RF HT ($n = 189$), intracavitary MW HT ($n = 39$) or whole-body HT (WBH) using infrared radiant heat devices ($n = 20$), in combination with radiation, chemotherapy or both. A control group was included in six studies that showed a longer OS in the HT groups than in the control groups: 11.7 vs. 5.6 months. In three studies with a control group, the overall response rate was also improved for the HT groups: 43.9% vs. 35.3%. Finally, the BSD applicators Sigma-30/40/60 were used in combination with CT to treat children with refractory or recurrent non-testicular malignant germ-cell tumors that failed a standard cisplatin regimen [8]. The new chemo regimen was based on a combination of cisplatin, etoposide, and ifosfamide, also known as PEI regimen. The treatment also included surgical resection or radiation to patients with incomplete tumor resection. Of the 35 patients who had sufficient data available for response assessment, 86% had an objective response to treatment and the 5-year OS was 72%. This multimodal treatment using regional HT proved to successfully treat children and adolescents with refractory or recurrent malignant non-testicular germ-cell tumors.

3.9. Summary of clinical trials

The use of MW/RF HT in combination with different chemotherapy regimens has proved its merit and warrants further investigation. Table 3 lists all active Phase I/II, Phase II, and Phase III trials that are exploring the use of MW/RF HT, either radiative or capacitive, in combination with chemotherapy or immunotherapy regimens. We used these criteria and performed a search in the ClinicalTrials.gov using “cancer” under “Condition or disease” and “(immunotherapy OR chemotherapy)

Table 3
Active phase II and III clinical trials that combined adjuvant hyperthermia therapy (HT) with chemotherapy (CT) or chemoradiotherapy (CRT) using RF/MW hyperthermia devices.

Clinical trial (estimated dates)	Trial design	N	Arms	Device	Drugs	Disease
NCT-01077427 (2012−2021)	III, R	336	CT ± HT	BSD-2000 3D ± MR	Gemcitabine Capecitabine Cisplatin	Resected pancreatic adenocarcinoma
NCT-01716949 (2012–2021)	I/II, R	59	CRT ± HT	BSD-2000 3D ± MR	5-Fluorouracil Capecitabine Oxaliplatin	Primary locally advanced/recurrent rectal cancer
NCT-02369939 (2014–2021)	III, R	118	CRT ± HT	BSD-2000 3D ± MR	Mitomycin C 5-Fluorouracil	Anal carcinoma
NCT-03332069 (2014–2019)	III, R	236	CRT ± HT	EHY-2000+	Cisplatin	Locally advanced cervical cancer
NCT-02359474 (2015-N/A)	III, R	120	CT ± HT	BSD-2000 3D ± MR	Trabectedin	Advanced soft-tissue Sarcoma
NCT-02567383 (2015–2020)	II, single-arm	45	CRT + HT	Thermotron RF-8	Cisplatin Taxotere	Recurrent head and neck cancer
NCT-02862015 (2016–2019)	II, R	100	CT ± HT	EHY-2000+	Folfirinox Gemcitabine	Metastatic pancreatic cancer
NCT-02439593 (2017–2021)	II, R	78	CRT ± HT	BSD-2000 & BSD-2000 3D	Gemcitabine	Locally advanced pancreatic cancer
NCT-03249519 (2017-N/A)	N/A, single-arm	N/A	CRT ± HT	BSD-2000 & BSD-2000 3D	Cisplatin	Advanced cervical cancer
NCT-03393858 (2017–2020)	I/II, single-arm	40	IT + HT	Thermotron RF-8EX	Anti-PD-1 antibody Biological: DC-CIK IT	Advanced malignant mesothelioma
NCT-03561142 (2018–2024)	II, single-arm	94	CRT + HT	BSD-2000 3D ± MR	5-Fluorouracil Oxaliplatin Folinic acid	Locally advanced rectal cancer
NCT-03757858 (2018–2020)	I/II, NR	80	IT ± HT	Thermotron RF-8	Anti-PD-1 antibody Adoptive cellular IT	Abdominal and Pelvic Malignancies or Metastases
NCT-03335059 (2019–2025)	III, single-arm	106	CT + HT	Synergo SB-TS 101	Mitomycin C	Non-muscle invasive bladder cancer
NCT04172675 (2020−2022)	II, R	280	CT ± HT	Synergo SB-TS 101	Erdafitinib Gemcitabine, Mitomycin C	Non-muscle invasive bladder cancer
NCT03249519 Recruiting	N/A	N/A	CRT ± HT	BSD-500 interstitial	Cisplatin	Cervical cancer

N, estimated patient enrollment; N/A, data not available; R, randomized; NR, non-randomized; IT, immunotherapy; PD-1, Programmed cell death protein 1; DC-CIK, dendritic cells mixed with cytokine-induced killer cells.

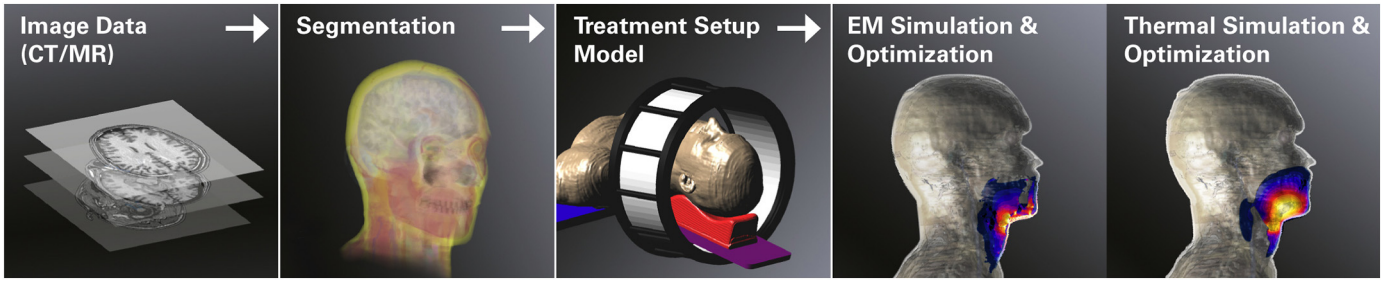


Fig. 3. Hyperthermia Treatment Planning (HTP) workflow. Reprinted from [54].

AND hyperthermia" under "Other terms" on March 16, 2020. This search yield 241 clinical trials, of which the vast majority were either related to hyperthermic chemoperfusion methods or included some synonymous of hyperthermia (fever, febrile, temperature elevation, or heat treatment) not related to a cancer treatment. The other trials excluded from the list used focused ultrasound and laser hyperthermia.

4. Potential for RF and microwave mediated hyperthermia and drug delivery

Current RF/MW hyperthermia treatments are driven by qualitative patient complaints and are limited by very few measured temperature points. In order to make a more complete and quantitative assessment of the heated treatment field, there are two avenues that can extend our knowledge of the applied energy (SAR in W/kg) and temperature distributions in tissue: computer simulations and magnetic resonance (MR) thermometry. Computer simulations use numerical methods 3D patient-specific anatomical models to generate SAR and temperature maps. The simulations are typically used to generate a pre-treatment plan, but the same tools are also used for online treatment guidance. Such simulation-guided HT uses a feedback optimization scheme that is updated with the signals applied to the antennas, the measured temperatures, and feedback from patients, so that treatment settings are adapted in real-time to optimize the treatment delivery [85]. The most advanced thermal assessment for HT is MR thermometry (MRT), which provides 3D temperature maps superimposed with the patient anatomy [128]. Ishihara et al. developed the framework for the most used method to calculate MRT, the proton resonance frequency shift method [129]. This method allows to obtain MRT maps from MR phase data [130]. These maps are currently obtained about every 10 min or 15 min and only now are starting to be used in HT treatment guidance. The last possible iteration of MR-HT guidance is to combine simulations with MRT, thus providing the ultimate level of dosimetry before, during and after treatment. These tools facilitate rigorous temperature control and simulation-based heating adjustment possibilities, which is a requirement for optimal enhancement of drug delivery of conventional systemic chemotherapy and/or temperature mediated drugs [74].

4.1. Simulation-guided hyperthermia

Clinical application of HT is usually delivered after performing patient-specific HT treatment planning (HTP) [54,55]. The latest advancements on HTP have been driven by enhanced computer capabilities and recent advancement in computational algorithms. The HTP process begins by acquiring 3D images of the patient anatomy comprising the treatment volume, obtained from computed tomography and/or magnetic resonance imaging (MRI). The following step is to delineate the different tissues, where the required number of tissues and the level of detail of the delineation depends on the desired accuracy, which varies for each application. For deep HT, the tissues usually segmented include muscle, fat, bone and internal air [131]. Head and neck treatments involve more critical structures that 11 additional tissues are discriminated [132]. The end result is a patients-specific model that will feed the simulation phase.

In the next step, the patient virtual model is imported into a multiphysics simulation software that already has the virtual HT applicator design. Then, dielectric and thermal properties are assigned to each tissue, including physiological parameters like blood perfusion rate (units of kg/s/m^3) and metabolic heat generation rate (units of W/m^3). The final step is then to perform the SAR and temperature simulations and optimize the antenna parameters to target the patient tumor. The Pennes bioheat method is commonly used to compute the temperature profile in the tissue [33]. The position of the patient model relative to the applicator will be documented and should be reproduced during the actual treatment to deliver the planned optimized treatment. Fig. 3 shows the Schematic workflow for EM-HTP, using head and neck hyperthermia as an example.

The patient-specific HTP is a robust tool for treatment decision making, i.e., whether to treat or not, since it facilitates evaluating the ability to heat a specific tumor and to identify potential hotspots before performing the treatment. In addition, HTP can help physicians to conduct the treatment and perform real-time adaptations to the treatment to respond to patient complaints. Besides treatment planning and optimization, HTP is also a valuable tool for the development of medical devices, training of HT personnel, and post-treatment dosimetry to evaluate the delivered treatment strategy. The only commercial package for HTP currently available is HyperPlan (Sennewald Medizintechnik, Munich, Germany), which allows to optimize treatment settings using electromagnetic and thermal simulators for the BSD-2000 applicator series. More general electromagnetic and thermal solvers like Sim4Life (ZMT Zurich MedTech AG, Zurich, Switzerland), CST Studio Suite (Dassault Systèmes, Vélizy-Villacoublay Cedex, France) and ANSYS (Canonsburg, Pennsylvania, US) are also used to perform electromagnetic and thermal simulations.

HT treatment guidance using real-time simulations has greatly benefited from the introduction of various HTP platforms, including VEDO, the visualization tool for electromagnetic dosimetry and optimization [133], and Plan2Heat [134]. In a retrospective analysis of treatment reports of 35 patients treated with deep HT controlled by extensive treatment planning, it was demonstrated, that HTP is able to provide a global indication of the regions where hotspots during treatment will most likely occur [135]. A recent advancement of HTP, is patient-complaint guided steering, where heating is steered from a region of complaint by adding constraint factors for that region. Amplitude and phase of each individual element can be re-optimized to maintain the optimum tumor dose while minimizing the heating in the area of complaint [131,133,134].

4.2. Mr-guided hyperthermia

HT treatments are monitored using a limited number of superficial or invasive thermometry probes using stationary measurements or measuring along the implanted catheter track. In time, MRI has

developed from a diagnostic imaging tool into a treatment guidance modality, i.e., magnetic resonance thermometry (MRT) [136]. MRT provides the option of 3D non-invasive temperature monitoring of the full treatment region, including tumor and surrounding tissues. Hence, MR-HT hybrid systems can operate within the MR bore to facilitate MRT during treatment. Besides providing assurance of effective steering, the 3D temperature data is also used to evaluate hotspots, i.e., regions that are getting too hot in healthy tissue. The operator can then adjust the heating patterns to protect healthy tissue and avoid patient discomfort and pain that, if unaccounted for, may lead to unwanted side effects such as burns. An example of MR-guided hyperthermia is illustrated in Fig. 4.

Besides temperature monitoring, MRI is being explored to capture other patient parameters relevant for HT, including electrical tissue properties [137], diffusion [138] and blood perfusion [139,140]. At the moment, HTP simulations are based on parameters from literature, which are typically the result of an average of limited data and measured ex vivo. Thus, acquiring of the 3D patient-specific properties, together with accurate and reproducible patient positioning, makes the use of MR a very attractive addition to HT treatments. Finally, MR can also accurately reproduce changes of body shape due to pressure of the water bolus for a more accurate modelling of tissue position relative to the applicator [141]. To this date, MR-HT systems are only available for deep HT, and it use has been reported for the treatment of pelvic and extremities tumors (BSD2000-3D/MR) [128,142,143] and lower extremities (MAPA) [144–146]. An extensive review of clinical and preclinical MR-HT applicators can be found in [147,148].

MR can also be a relevant tool to validate mathematical models, which are being evaluated to predict the effect of HT and specific chemotherapeutic agents. A recent study with heat-shock response models support the belief that the combination of HT with bortezomib, a clinically approved proteasome inhibitor, increase therapy efficacy [149]. Mathematical models are also being developed to predict the spatial drug delivery profile of temperature sensitive liposomes [150,151]. The combination of improved modelling approaches, more powerful and faster computations and real-time monitoring will accelerate the evolution of HTP leading to improved delivery of clinical HT treatments. Some of the current main limitations of MRT include the high cost of the MR system and difficulty in maintaining stable temperature measurements over long durations ~60–90 min due to motion artifacts (respiratory motion, organ motion and air travelling), and magnetic field drift artifacts [130,152].

The advancement of MR monitoring will facilitate the optimization of temperature kinetics of drugs to deliver a local treatment. Automatic MR-based feedback loop control are currently being evaluated to adapt the hyperthermia treatment for a patient specific session [147]. This aims to optimize the treatment with the objective of delivering the best thermal dose while preventing the generation of treatment limiting undesired hotspots. Hence, MR-guided HT can play an unprecedented role in localizing heat that can be tailored to temperature sensitive nanocarriers loaded with a chemo- or immunotherapy payload. This multimodality treatment can lead to significantly more targeted drug delivery and reduce side effects, which can facilitate increasing the number of patients treated with thermochemotherapy or thermoimmunotherapy.

5. Future outlook

RF and MW HT devices have been the golden standard for clinical studies using thermal therapies for multi-modality cancer treatment. Yet, thermal dose-effect studies indicate that an even higher therapeutic outcome is achievable when higher temperatures are reached. In this review, we report on devices that use higher frequency EM waves, i.e. MW and RF, which are under development and/or being translated into the clinic [59,71,153–156]. These devices can induce a smaller heat focus then current RF based systems [157,158], which can be dynamically adjusted to conformal heating of irregular target regions [159].

Target conformal heating requires tight dose monitoring to ensure that the heat focus is precisely aimed and maintained at the target region. Hence, researchers are investigating improved approaches for (real-time) and 3D dosimetry. As explained, treatment planning has matured and is being studied for pre-treatment planning as well as for real-time guidance. In addition, following an earlier clinical adoption in (FUS-induced) ablation therapy [160,161], MRT is slowly starting to make its mark also in HT. The developments in simulation and MRT guided treatment are expected to reinforce each other since MRT forms the tool required to validate treatment planning in 3D. In addition, validated treatment planning simulations not only provide the tool for guiding treatment but also provides the tool to design better applicators, create treatment and quality assurance guidelines, perform better training and develop new treatment approaches. Following these developments, and in view of cost and complexity of treatment, we expect that two distinct approaches will appear that will co-exist:

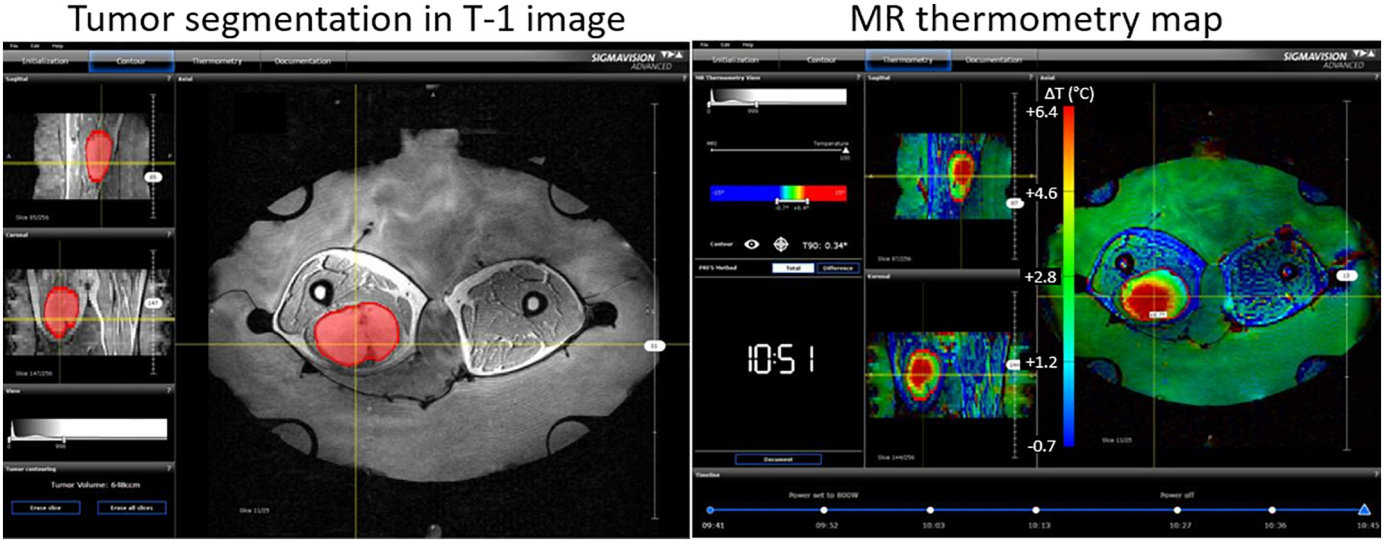


Fig. 4. Example of MR guided hyperthermia. The left panel shows the T-1 image with the delineated sarcoma on the leg, the right panel shows the MR-thermometry map at the end of the treatment. Courtesy of Dr. Sennewald Medizintechnik GmbH (Germany).

1) the simulation-adaptive HT approach that provides a relatively low-cost means to stimulate a range of cytotoxic drugs and 2) a personalized high-precision MR-adaptive approach based on advanced MR-guided HT.

Simulation-adaptive HT will be based on HT with RF or MW techniques and will exploit our increasing knowledge of thermoregulation. This knowledge will be included into advanced treatment planning software tools to pre-plan the treatment and perform real-time guidance. Monitoring will be based on a combination of interstitial, intraluminal and/or intracavitary thermometry with 3D treatment planning. To improve the effectiveness of the combination of HT and drugs, this line would strongly benefit from advancing our knowledge on temperature dependent perfusion to enable optimizing the temperature distribution. This approach already exists in the academic setting and will be improved to speed-up the learning curve for new clinics entering this field. In addition, approaches like automatic segmentation will reduce the time-consuming labor of treatment planning and the required expertise, thus facilitating smooth dissemination of simulation-adaptive HT to non-academic clinics.

The most advanced high-precision MR-adaptive HT, will probably remain an approach for academic centers in the upcoming decade. The utility of MR-adaptive HT is still in its infancy and its development will be strongly correlated with progress in MRT, especially in regions where measurements are affected by respiratory, cardiac or peristaltic driven motion or other actions that imply organ/tissue movement such as swallowing. Hence, MRT guided HT crucially depends on motion-robust MRT at an accuracy better than 1 °C [162–164] since the aim is to increase temperature by only 3–7 °C. The maximum achievable accuracy of MRT is dictated strongly by the time required to capture a full MRT scan. For anatomical MR imaging, averaging of multiple measurements is usually used to obtain the required signal-to-noise ratio (SNR) per scan [165]. This approach is not possible for MRT since averaging effects (over a single scan) should be minimized as they will increase motion artifacts and reduce the temporal accuracy of the temperature measurements. In this respect, first generation MR-HT systems are using the body coil of the MR scanner leading to a limited SNR performance [166]. More recent approaches use dedicated imaging coils nearby the skin of the patient for higher SNR as well as exploitation of faster, i.e. parallel, imaging approaches, which are based on the spatial differences between receive coil sensitivities. Recent investigation have also explored different MR excitation schemes to accelerate image reconstruction in 2D and 3D [167,168], and to monitor temperature changes in fatty and aqueous tissue simultaneously [169]. The actual improvement of these methods for the hyperthermia application are yet to be validated in the clinical setting.

MRI has other features of which the utility for controlling HT is currently being investigated. Firstly, MRI provides anatomy contrast that is unprecedented in the imaging field. Hence, MRI is optimally suited to verify patient positioning inside the applicator, as basis for adapting treatment planning in real-time and to monitor the tumor regression/progression during the course of therapy. In addition, a range of MRI techniques exist, with or without contrast enhancement, to visualize physiological properties like blood perfusion during therapy. When applied in conjunction with chemotherapy, this approach might enable feedback-controlled image-guided drug delivery approaches. Hence, MR guided therapy is especially beneficial when used to sensitize for drugs and/or improve delivery homogeneity.

MR-guidance may play another important role when using thermosensitive liposomes [74]. These liposomes can be filled with a mix of MR contrast fluid and drugs for calibrating the MRT [170] or for close drug delivery monitoring. Note that the validity of the latter approach for monitoring drug delivery is determined by the similarity in diffusion depth from vessel into the tissue of the molecules for monitoring and delivery. Note also that MRT accuracy can be affected by paramagnetic contrast agents [171]. Still, recent studies have shown that, at ultra-high-field MRI (≥7 T), visualizing metabolism is possible to more precisely track tumor activity [172]. This approach can even be enhanced when expanding the imaging to more multi-nuclei, i.e., using not only hydrogen but also phosphorus atoms, which provides information similar to positron emission tomography (PET) and may also improve MRT [173]. Pre-clinical evidence suggests that this may strongly enhance sensitivity for aberrant metabolism, which is known to correlate with tumor aggressiveness. However, whether MR-HT devices can deliver on this potential is currently unknown. Still, there are many opportunities for MR-adaptive HT using the plethora of anatomical, physiological and metabolic MRI contrasts. The MR-guided RF and MW HT devices currently under development provide solid bases to study the benefit of all of these approaches independently, as well as combined.

In summary, RF techniques are usually used when HT is combined with chemotherapy. The current level of quality and success of the described clinical trials provides a solid basis since they showed significantly improved therapeutic results. In contradiction to radiotherapy with HT, thermal dose-effect studies have yet not been conducted so the optimum temperature (range) for application of hyperthermia is yet to be determined. In addition, not only temperature but also perfusion may well be highly important to assess HT effectiveness. In this respect, the advent of novel MR-guided devices provides many new perspectives, which will help to elucidate thermal or perfusion dose-effect relations. Integrated device and coil design, as well as new heating devices and temperature / perfusion measurement strategies should be developed to enable highly controlled application of HT. Given recent progress in these topics, combined with the advancements on temperature mediated drugs, we expect that the upcoming decade will bring breakthroughs in our knowledge, leading to optimized HT approaches for cancer patients.

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