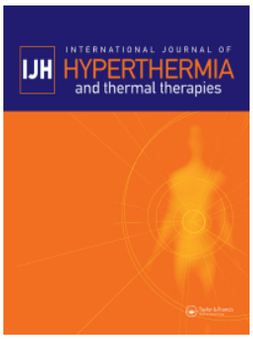

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Evolving technology for thermal therapy of cancer

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Abstract
This paper is intended as a succinct review of technology used for clinical hyperthermia therapy for cancer, as culled from a presentation at the special workshop on Thermal Medicine, Heat Shock Proteins, and Cancer at the Society for Thermal Medicine conference in Spring 2005. Following a brief overview of thermal therapy treatment options and available mechanisms for heating tissue, the paper focuses on the evolution of equipment from basic single element heating devices of the early 1980s to adjustable multi-element heating devices currently in use or in final stages of development. Representative devices from the past, present and near future are cited for further investigation by the interested reader. The paper concludes with a summary of general trends in the evolution of clinical hyperthermia techniques and a statement of current challenges remaining for the field.

Keywords: *Thermal therapy, hyperthermia technology, heating equipment*

Introduction

Thermal medicine may be considered to encompass all treatments based on the transfer of heat energy into or out of body tissues to accomplish a therapeutic result. Numerous clinical applications for heating and cooling tissue have been identified, including the reduction of pain or inflammation, wound healing, organ preservation, thermal surgery and cancer therapy. While the classifications presented in Figure 1 are approximate and overlapping, this general guideline differentiates mechanisms of interaction of heat and cold with living tissue and identifies techniques used to accomplish therapy over the specified temperature ranges. Thermal therapy may be performed either with cryotherapy ($<-50^\circ$C for >10 min); moderate cooling (0–10°C for 10 min, often repeated after short breaks); or at three overlapping but characteristically different regimens of elevated temperature: low temperature hyperthermia (39–41°C for times up to 72 h); moderate temperature hyperthermia (42–45°C for 15–60 min, usually repeated for multiple fractions to achieve higher cumulative thermal dose); and high temperature thermal ablation therapy

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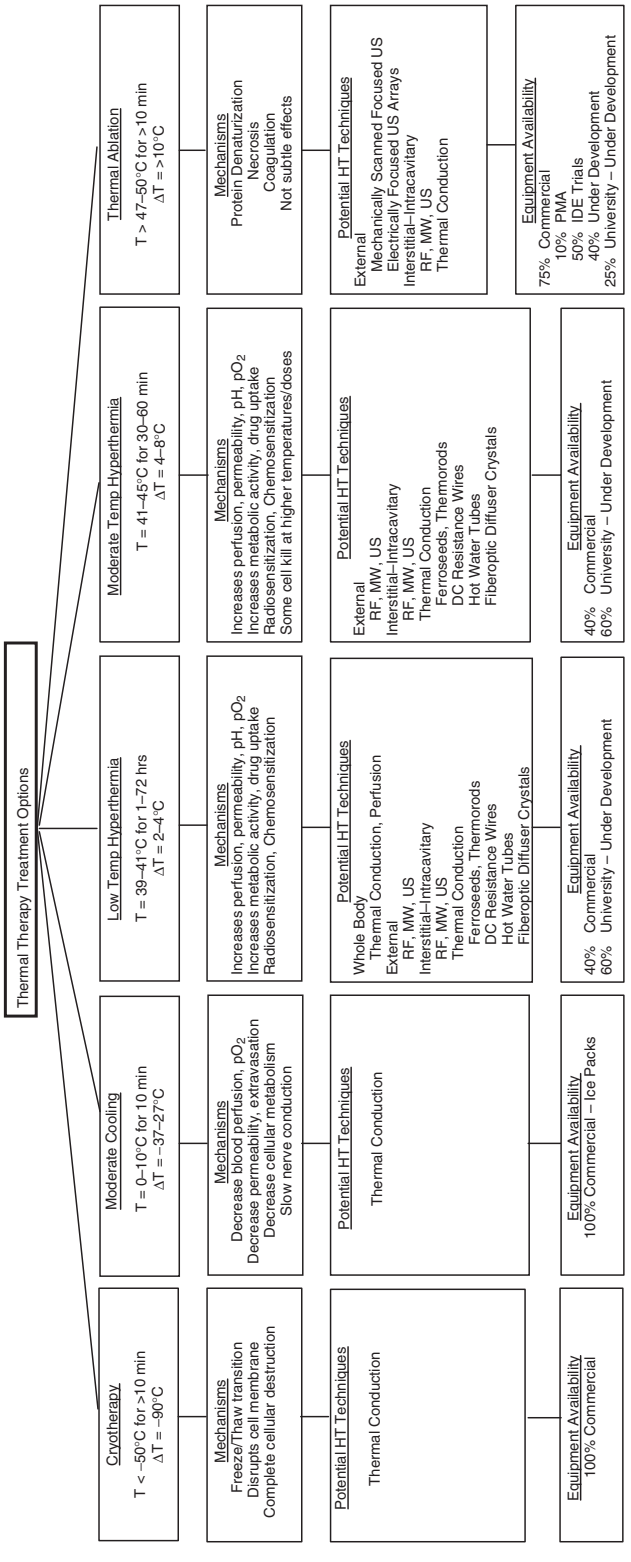

Figure 1. Treatment options for therapeutic use of thermal medicine.

(usually >50°C for >4–6 min). Mechanisms by which these five general therapeutic approaches interact with tissue differ as indicated in Figure 1, ranging from transient subtle increases or decreases in blood perfusion, tissue oxygenation and cellular metabolism for the central three therapeutic regimens, to rapid irreversible effects such as complete vascular stasis, protein denaturization, cellular coagulation and tissue necrosis for the more extreme cryotherapy and thermal ablation approaches.

Following a brief overview of thermal therapy treatment options, this presentation will focus on the heating technology used for clinical hyperthermia therapy for cancer—the Moderate Temperature and Low Temperature Hyperthermia options listed in Figure 1. Thermometry approaches and thermal surgery options such as cryotherapy and high temperature ablation will be covered separately; a review of thermal ablation technology by Diederich follows this presentation. Similarly, invasive thermometry approaches have been reviewed previously [1–4] and non-invasive thermometry techniques will be addressed by Wust in a subsequent special issue of this journal. While impossible to mention all devices of merit, this review will briefly characterize available heating modalities and cite representative applicator types that have proven useful in the clinic to date. The paper will end with a summary of general trends in the evolution of clinical hyperthermia techniques and a statement of current challenges remaining for the field.

Mechanisms of heating

While there are countless devices and techniques for heating tissue, they all derive from three basic mechanisms for delivering heat energy to the body:

(i) *Thermal conduction of heat*, which flows from higher to lower temperature at a rate dependent on the thermal gradient and thermal properties of all contacting material.

(ii) *Resistive or dielectric losses from an applied electromagnetic (EM) field*. At radiofrequencies below ~20 MHz, an EM field between implanted or surface contacting electrodes induces a net movement of electrons. The induced currents deposit power from I^2R resistive losses, with the highest power deposition occurring in tissues with the highest current density. At microwave frequencies above ~100 MHz, the radiative mode of EM propagation and dielectric losses in tissue predominate over conduction current losses. Under these conditions, heating results from friction between adjacent polar water molecules which oscillate in response to the time varying field. For both radiofrequency (RF) current and microwave (MW) radiation, absorbed power density (SAR) decreases exponentially with depth in tissue. Critical factors in selecting most appropriate EM frequency are tumour size and depth relative to EM wavelength. For practical frequencies used in hyperthermia, the wavelengths in soft tissue vary from a tumour-sized 4.5 cm at 1000 MHz up to 30 m or more at the lower RF frequencies. The maximum spatial resolution of power deposition (focal spot size) is approximately half this wavelength so that low frequency RF may be used to penetrate but not to focus energy at depth. Higher frequencies may be used to focus heat into tumour sized volumes but exhibit higher attenuation that restricts penetration.

(iii) *Mechanical losses due to molecular collisions from an applied ultrasound (US) pressure wave*. Similar to EM radiation, ultrasound intensity decreases exponentially with depth in tissue, with a trade-off between effective localization of power superficially at the higher frequencies and deeper penetration due to decreased attenuation at the lower frequencies. The most useful frequencies for depositing power in human sized

anatomy ($f = 0.5$–10 MHz) have wavelengths ranging from $\lambda = 0.1$–3 mm which are much shorter than the dimensions of both tumours and applicators. Thus, dispersion of the beam is minimal and well-collimated beams may be directed into tumour size volumes. Due to the combination of short wavelength and low attenuation, US sources can be used to penetrate deep in the body while still focusing into small tumours.

The underlying physical principles of these heating mechanisms have been described in a number of excellent review articles [5–8] and in books covering the field of hyperthermia in general [4, 9–11].

Devices and techniques for heating tissue

Over the past three decades, hundreds of devices and techniques have been investigated for use in clinical hyperthermia. Although some have been studied only theoretically, most have been reduced to practice and thoroughly tested at University research facilities. Many have demonstrated useful heating patterns for a sufficient number of patients that prototype equipment was commercialized and distributed to multiple institutions. In other cases, prototype systems have demonstrated effective heating capabilities at one institution but still await distribution, pending enhanced clinical demand sufficient to justify commercialization. Typically, heating techniques are categorized as either Whole Body, Regional, Superficial or Interstitial/Intracavitary. These technologies have been reviewed numerous times [1, 4, 10, 12–16]. The following sections briefly categorize the available heating modalities and reference representative techniques from among the most common approaches used in the early days of hyperthermia, in contrast to the more sophisticated equipment available today.

Whole body heating

Early attempts at *fever therapy* [17] notwithstanding, systemic heating is generally accomplished with thermal conduction heat sources such as immersion in *heated fluids* [18, 19], *heated air* [20, 21] or wrapping the patient in *heated blankets* [22]. Some investigators have attempted to speed up heating using supplemental RF regional heating devices [23, 24], although this increases temperature variation within the body and treatment complexity. Others have used invasive approaches such as *extra-corporeal circulation* of heated blood through exteriorized arterio-venus shunts [25].

Deep regional heating techniques

While several large ultrasound array devices have been designed for deep tissue, large volume hyperthermia [26–30], most ultrasound equipment is used to focus heat into smaller volumes at depth due to the short wavelength of typical 1–5 MHz systems. Focused ultrasound has been used successfully for several deep tissue thermal ablation applications [31, 32], as described by Diederich in an accompanying paper of this volume. To heat large tumour volumes at depth, electromagnetic fields in the range of 10–120 MHz are generally used with wavelengths that are long compared to body dimensions and, thus, deposit energy over a sizeable region. Early hyperthermia trials were conducted with single aperture devices having no ability to steer or focus energy other than by shifting patient position relative to the applicator, such as the 27 MHz *Ridged Waveguide* [33], 82 MHz *Helix* [23] and

Magnetrode (Henry Radio, Los Angeles, CA) magnetic induction coil [34, 35] systems and somewhat later the 70 MHz *Coaxial TEM applicator* [36–38]. The most extensively used single channel EM device is the *Thermotron RF-8* (Yamamoto Vinyter, Japan) with two capacitive plate electrodes mounted on opposing arms of a rotating gantry [39, 40]. Using different size electrodes, RF currents are concentrated under the smaller electrode. Ongoing clinical use primarily in Asia has demonstrated the ability to heat at the lower end of the hyperthermic range in patients with sufficiently thin layers of high resistance fat tissue overlying tumour, using aggressive skin cooling [41–44]. Another novel approach called *Magnetic Fluid Hyperthermia (MFH)* uses injected magnetic nanoparticles to localize heating at depth in the body when the region is immersed in an external 100 KHz magnetic field [45, 46].

With the goal of increasing control over power deposition at depth, several large electromagnetic array applicators have been developed. One of the first was the 60–120 MHz *Annular Phased Array (APAS)* system (BSD Medical Corp, Salt Lake City, UT) which consisted of eight equal power equal phase dipole antennas mounted concentrically around a torso-sized inflatable water bolus-coupled opening [47]. Although capable of clinically useful regional warming within patient tolerance, these early phased array systems lacked 3D adjustability and could not localize heat within an entire tumour volumes at depth [48–50]. Improved SAR adjustment was possible with the 70 MHz *Matched Phased Array (MPA)* four waveguide applicator [51] and the extensively used *Sigma 60* applicator, which adds four independent phase and amplitude controls and an improved patient interface to the previous eight dipole APAS system. While Sigma 60 applicators have demonstrated significantly improved clinical utility [52, 53] and are in clinical use today, the next quantum step towards improved steering of power deposition at depth was provided by the *SigmaEye* applicators. These applicators operate at the same frequencies as the predecessor Sigma 60, but include three rings of eight dipoles each and 12 independent phase and amplitude adjustments to shape and steer power deposition peaks axially and radially around the body interior. An MRI compatible version of the system facilitates pre-treatment planning as well as real-time MRI monitoring of deep tissue temperature and physiologic change during treatment [54–56]. Recent clinical results have demonstrated the correlation of non-invasive MR thermography with direct tumour temperature measurements and clinical response [57]. Efforts are well underway to bring further improvements in phase and amplitude steering into the clinic with the 12 water-coated antenna applicator (WACOA) for MR-controlled deep-body hyperthermia [58].

Superficial heating technology

In general, EM techniques are used to treat superficial disease less than 2 cm from the surface while deeper penetrating ultrasound is used for tumours extending down to ~4–6 cm below the surface. Initially, the most common applicator was the *microwave waveguide*, a rectangular or circular metal structure that guides EM waves from a single monopole feed to an open aperture at least a half wavelength in largest dimension that radiates TE_{10} mode waves. Waveguide antennas are commercially available in sizes from 7.5–24 cm, generally for use at ISM band frequencies of 915 or 2450 MHz in the US [59–61] or at 430–434 MHz in Europe and Japan [62, 63]. Coupling of EM radiation from waveguide antennas into tissue is generally improved with a thin layer of temperature controlled deionized water or mineral oil bolus, although care must be taken to select the

appropriate size and thickness of bolus to avoid perturbations of the EM field [60, 64, 65]. In general, single aperture waveguides produce effective heating >50%SAR_{max} covering only 30–60% of the aperture face and are not adjustable. Early clinical trials demonstrated that these sources were effective only for lesions up to ~3cm diameter [66]. That conclusion from early clinical trials spawned the development of numerous new approaches for treating larger area disease, including custom-sized arrays of 433 MHz *Current Sheet Applicators (CSA)* [67] and *Lucite Cone Applicators (LCA)* [68, 69], which are in clinical use today in Europe. Another approach that has been used successfully in the clinic involves computer controlled mechanical rotation of one or two *Scanning Spiral Microstrip Antennae* over surface disease [70, 71]. The largest surface applicators used clinically to date are the 25 aperture 915 MHz *Spiral Microstrip Array* developed at Stanford University [72] and the *Conformal Microwave Array (CMA)* applicator developed at the University of California San Francisco [1, 73–76]. While the Stanford spiral antennas were used successfully in a large clinical experience [71, 77, 78], the applicators were never commercialized. Similarly, while initial clinical evaluation of CMA applicators has been promising in terms of heating uniformity and patient acceptance, the authors suggest that continued development of thermal monitoring approaches is necessary for control of large 32 element arrays [1, 76, 79]. The same group reports ongoing development of a related *Combination Applicator* that should facilitate treatment of superficial disease with heat and brachytherapy radiation simultaneously using the same flexible PCB based conformal array applicator [80–82]. A third large area flexible PCB micro-strip-based surface applicator, the *Contact Flexible Microstrip Applicator (CFMA)*, is currently under development for use at 433 MHz in Europe [83, 84]. With the exception of the most basic microwave waveguide antennas, all of the above University developed systems appear useful for clinical treatment of surface disease but are not yet available commercially.

A similar evolution of superficial heating devices has occurred with US technology. Early efforts used single disk degassed water-coupled 'piston' transducers operating at 0.5–3.5 MHz [85]. With no potential to adjust SAR pattern, the lightly focused US transducers were capable of heating only small superficial lesions. Subsequently, improved lateral extent and control of heating was provided with the 16 transducer planar array *Sonotherm 1000* (Labthermics Technologies Inc, Champaign, IL) applicator, which has seen extensive clinical use treating disease up to $15 \times 15 \times 6$ cm [86] and is still available commercially. For somewhat deeper penetration, a *Focused Ultrasound Array* [87] device used in early clinical studies led to subsequent construction of a *Scanned Focused Ultrasound System* with an array of 1 MHz transducers directed to a small focal spot that is mechanically scanned around the tumour volume [27]. This device was used successfully for clinical treatment of tumours in the pelvis, abdomen and even brain. After adding less penetrating 4 MHz transducers and a patient pain feedback button to turn off power during portions of the scan path, even higher average tumour temperatures were obtained [88]. While technically demanding, this mechanically scanned focused ultrasound approach appears extremely promising, although commercial distribution of such a system has not been attempted yet. Another innovative approach involves use of two different frequency arrays of US transducers aimed laterally across a thin water bolus layer at a triangular shaped reflector which redirects energy down into the tumour. The *Scanning Ultrasound Reflector Linear Array System (SURLAS)* [89, 90] scans the reflector cyclically under computer control across the tumour. Lateral SAR distribution is adjusted by computer modulation of power to each transducer, while effective penetration depth is adjusted by varying the relative amount of low and high frequency power.

Interstitial and intracavitary heating technology

As reviewed previously [91], there are at least nine distinct technologies for applying energy from miniature implantable heat sources and countless implementations of that technology in both University prototype and commercial form. Most common are coaxial cable mounted *MW antennas* [92] in a variety of dipole and/or helical coil configurations, *laser irradiated fibre-optic diffuser crystals* [93] and *RF electrodes* that couple either resistively [94, 95] or capacitively [96, 97] to surrounding tissue. For hyperthermia applications where temperatures are restricted to a narrow window, interstitially implanted sources heat roughly 1–2 cm diameter cylindrical volumes and, thus, are placed in arrays with <1–2 cm spacing. When high density implant arrays are clinically possible, even thermal conduction sources yield sufficient uniformity throughout the central portion of array. Thus, there has been considerable use of hot source techniques like needle- or catheter-based *Hot Water Perfusion (HWP)* [14, 15], *DC Resistance Wires (RW)* [98] and *Ferromagnetic Seeds (FMS)* [99, 100] which are unique in that no externalized connections are required to couple energy from an external magnetic field. Several approaches have been proposed to provide real-time adjustment of SAR along the implant length [101, 102]. Of the current interstitial systems, the most adjustable patterns are possible from the *MECS electrodes* [97] and *linear array tubular US transducers* in either direct coupled [103] or catheter-cooled [104] configurations. Recent enhancements to the ultrasound arrays allow control over angular as well as axial distribution of SAR [105]. Using one of the above technologies generally with somewhat larger diameter sources, numerous EM and US devices have been developed for heating tissue surrounding natural body cavities (e.g. urethra, rectum, oesophagus). Intracavitary heating technology has also been reviewed previously [4, 16]. Additional coverage of these techniques is provided in the high temperature thermal therapy article of this volume by Diederich and in a recent special issue on thermal ablation therapy [106].

Evolutionary trends in equipment development for hyperthermia

Over the past three decades, innumerable devices and techniques have been developed for heating tissue. Early efforts in the field of hyperthermia therapy for cancer attempted to treat tumours of vastly different size and depth in the body with a limited set of fixed aperture 'one technique fits all' equipment that eventually proved to have inadequate adjustability to accommodate variable tumour heating requirements. First generation equipment available for the early clinical trials of hyperthermia used simple structures (e.g. single aperture MW waveguide or piston US sources) with non-adjustable centrally peaked SAR patterns that could treat small volumes (e.g. 3–4 cm diameter) using 1–8 stationary temperature sensors to characterize the non-adjustable heating pattern. Second generation equipment became available in the 1990s with multi-aperture planar arrays and well-integrated computer monitoring and control interfaces that provided higher density thermal feedback and improved 2-D treatment planning to enable adjustment of heating patterns to fit a larger number of tumours. Over the past 5 years, the field has taken another quantum step forward and now offers a number of site-optimized applicators (e.g. CMA, CFMA, SigmaEye). These higher density multi-element phase and/or amplitude adjustable arrays are often coupled with more sophisticated treatment planning based on clinically realistic matching patient anatomic models and improved thermal feedback information from moving probe thermal mapping devices and/or non-invasive realtime 2D or 3D temperature distribution monitoring during treatment. Over the last 30 years, the field has progressed from single source hyperthermia applicators like those of Figure 2 to the multiple source approaches shown in Figure 3.

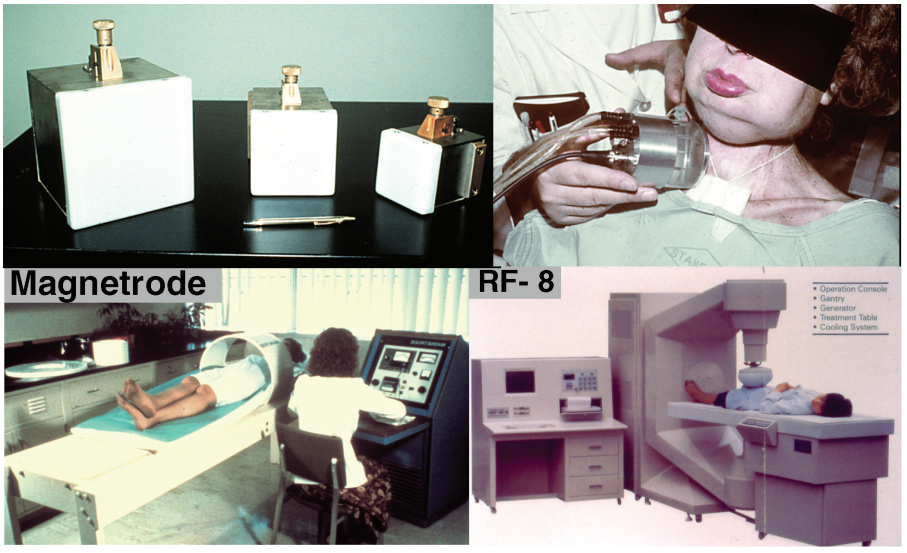

Figure 2. Single power source hyperthermia equipment used in hyperthermia therapy for cancer: 7.5, 10 and 15 cm square Clinitherm Corp. TE_{10} mode microwave waveguides, piston style ultrasound transducer, Henry Radio Magnetrode induction coil and Yamamoto Vinyter RF-8 capacitive plate heating system.

Summary and future directions

Technology for hyperthermia therapy of cancer has come a long way from clinical studies of the 1980s. Big improvements have been attained in both thermal monitoring and power control for real-time adjustment of heating distributions. Stationary one size fits all planar sources have given way to site-specific conformal arrays with custom fit patient interfaces and site-optimized mechanically scanned or electrically phase-focused arrays. Thermal monitoring is evolving from the recording of 1–8 fixed location temperatures to real-time feedback control based on high density thermal profile mapping and/or non-invasive real-time characterization of temperature and physiologic change distributions. Recent positive randomized clinical trials have demonstrated that existing devices can heat and indeed treat cancer effectively. Even so, many challenges remain before hyperthermia can become an accepted therapeutic modality. In terms of technology, the ongoing integration of non-invasive monitoring and control capabilities should be completed for the remainder of the evolving heating systems. Probably most critical for the future is that reimbursement rates be increased to match the current cost/benefit of hyperthermia therapy, to increase use of existing technology in appropriate clinical applications and to encourage equipment development for new clinical applications. Existing high performance equipment systems available only at one or two research institutions should be made available to other treatment centres to facilitate multi-institution clinical trials of new combination therapies as well as widespread application of already proven standard of care treatments. Finally, the training of new physicists and physicians must be accelerated to make more effective use of current technology. In summary, while a dramatic evolution of hyperthermia technology has provided significantly improved treatment capabilities, successful utilization of this new technology hinges on increased excitement about recent capabilities and positive clinical trials,

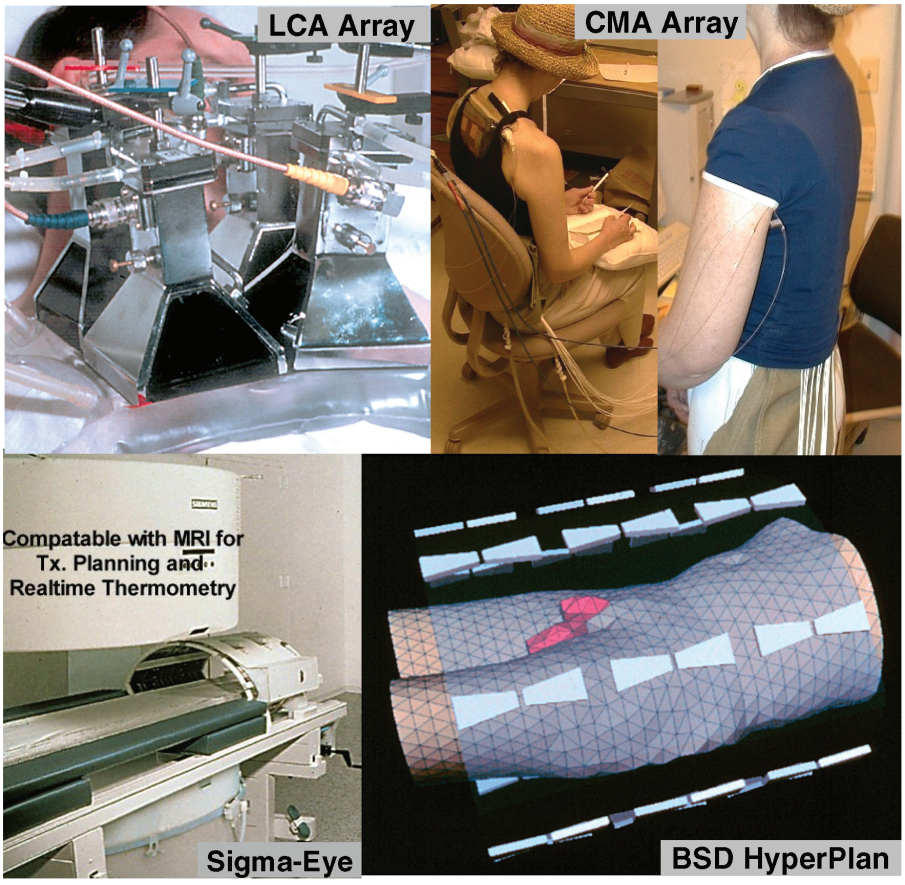

Figure 3. Multiple aperture heating systems including Lucite Cone Applicator (LCA) array treating chest, Conformal Microwave Array (CMA) applicator treating back and side and BSD Medical Corp. MRI compatible 24 antenna Sigma Eye deep heating system with HyperPlan treatment planning model for predicting optimum phase and amplitude settings to steer SAR into pelvic region tumour (in red).

more appropriate reimbursement, and significantly expanded commercial distribution and clinical utilization of the most recent higher performance equipment systems.

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