Thermal Therapy Techniques for Skin and Superficial Tissue Disease

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1. INTRODUCTION

There are numerous diseases and abnormal growths and conditions that afflict the skin and underlying superficial tissues. In addition to cancers such as primary, recurrent, and metastatic melanomas and carcinomas, there are many non-malignant conditions such as psoriasis plaques, port wine stains, warts, and superficial cut and burn wounds. Many of these clinical conditions have been shown responsive to treatment with thermal therapy - either low temperature freezing (cryotherapy),. moderate temperature warming to about 41-45°C (hyperthermia), or high temperature (>50°C) ablation or coagulation necrosis therapy. Because both very low and very high temperature therapies are for the most part non-selectively destructive in nature, they normally are used for applications where therapy can be localized precisely in the desired target and some necrosis of adjacent normal tissues is acceptable. With the exception of precision controlled cryotherapy or laser surgery (e.g. wart, mole, tattoo and port wine stain removal) or focal thermal surgery of small deep-seated nodules, it is generally preferred to use moderate thermal therapy (hyperthermia) in the treatment of skin and subcutaneous tissue disease in order to preserve the protective barrier characteristic of intact skin within the target region while inducing more subtle long term therapeutic improvement in the disease condition. This type of subtle thermal therapy is usually administered in combination with one or more other therapies such as radiation or chemotherapy - something with a differential effect on the target and surrounding normal tissues that can be magnified by the adjuvant use of heat.

1.1 Clinical Problem

As described above, there are numerous clinical problems occurring in the skin and superficial tissue which may benefit from the use of heat. Therapy of non-cancerous conditions of the skin with laser approaches is the subject of an accompanying article in this critical reviews proceedings. This review will focus on the devices and techniques available for thermal treatment of the following applications which may be considered representative of other adverse conditions of the skin and superficial tissues in terms of the requirements for heating technology:

- Hyperthermia therapy for primary, recurrent, or metastatic cancers of the breast, chestwall, skin, and tumor nodules within 2-3 cm of the tissue surface.
- Psoriasis plaques

Breast cancer is the most prevalent form of cancer in women, with an estimated 135,000 new cases reported in the USA in 1988 [1]. Unfortunately, locoregional failure of breast cancer treatments remains a devastating problem of increasing magnitude. The 5 year local control rate in Stage III breast cancer patients treated with either radiation, or combined radiation and chemotherapy following mastectomy is about 65% [2,3]. Although there is still a high incidence of in-field treatment failure, most patients with

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locoregional recurrence eventually die of metastatic disease. Local recurrence on the chestwall occurs in 3-22% of patients following mastectomy, depending mostly on the primary size and location, and adjuvant therapy [4]. The median survival following recurrence is only 2 years, though it ranges from a few months to 30 years [5]. Bedwinek et al [6] and others [7] have described failure to control locoregional recurrence of breast carcinoma as dramatically impairing the quality of life, with 62% of patients developing serious complications such as ulcerations, bleeding and pain requiring narcotics long before death. Clearly, a simple and effective adjuvant to current therapy for locoregional recurrence of breast cancer is needed to increase the duration of control and improve the quality of life for this large number of patients.

Psoriasis is a skin disease that afflicts approximately 2% of the population worldwide, or about 7 million Americans. There are numerous forms of psoriasis but the most common plaque psoriasis ranges from very small (1 x 1 x 0.3 cm) scaley lesions to extensive superficial disease covering from 10 to 100% of the body surface. While there is currently no cure for this condition which is characterized by a hyperproliferation of epidermal skin cells normally extending <3-5 mm in depth, numerous treatments are offered including topical medications (corticosteroid, vitamin or Anthralin creams and emulsions), oral chemotherapy agents (e.g. methotrexate), ultraviolet light therapy, and radiation treatments, in order to induce temporary remissions that last for varying lengths of time. Unfortunately, most treatments are expensive and accompanied by undesirable side effects. Hyperthermia has been demonstrated to be effective in eliminating psoriatic plaques with minimal side effects [8-11]. Although the complete responses are often transient like other treatments [8], most of the heat treatments have been applied with either waterbath or exothermic pads that effectively heat only the most superficial 1-2 mm of disease [8, 11, 12], or relatively small microwave or ultrasound devices that can heat deeper into tissue but have difficulty uniformly heating large areas of skin over contoured areas of the human anatomy [9, 10]. Again it is clear that a simple and inexpensive method of unifromly heating large areas of skin is sorely needed.

1.2 Effects of Heat

Local hyperthermia, delivered properly, has been shown to be an effective adjuvant to radiation and/or chemotherapy treatments for cancer. Biological data has explicitly shown that hyperthermia in the range of 42.5-45°C for 60 minutes produces pronounced cell killing alone [13-16] as well as synergistic interaction with radiation [17, 18] and chemotherapy [19, 20]. Studies with spontaneous tumors in anesthetized animals that could be treated with much higher thermal doses than are possible in alert human patients have demonstrated a strong correlation between minimum thermal dose and improved tumor response [21, 22]. Numerous clinical studies in patients with advanced or recurrent malignancies have also shown the addition of hyperthermia to radiation can dramatically improve tumor response rates [23-27]. Recently the potential benefits of moderate temperature hyperthermia have been summarized by treatment site for combinations with radiation and chemotherapy for cancer [28, 29]. An earlier review by Sneed and Phillips [30] summarized clinical results of hyperthermia combined with radiation and mentioned three very similar studies of chestwall recurrence cases which taken together demonstrated a complete response rate of 35% for lesions treated with radiation alone and 72% for those receiving radiation plus heat. While these initial clinical results showed improved response rates in tumors that could be heated as well as palliation and improved quality of life for the patients, they fell short of demonstrating significant

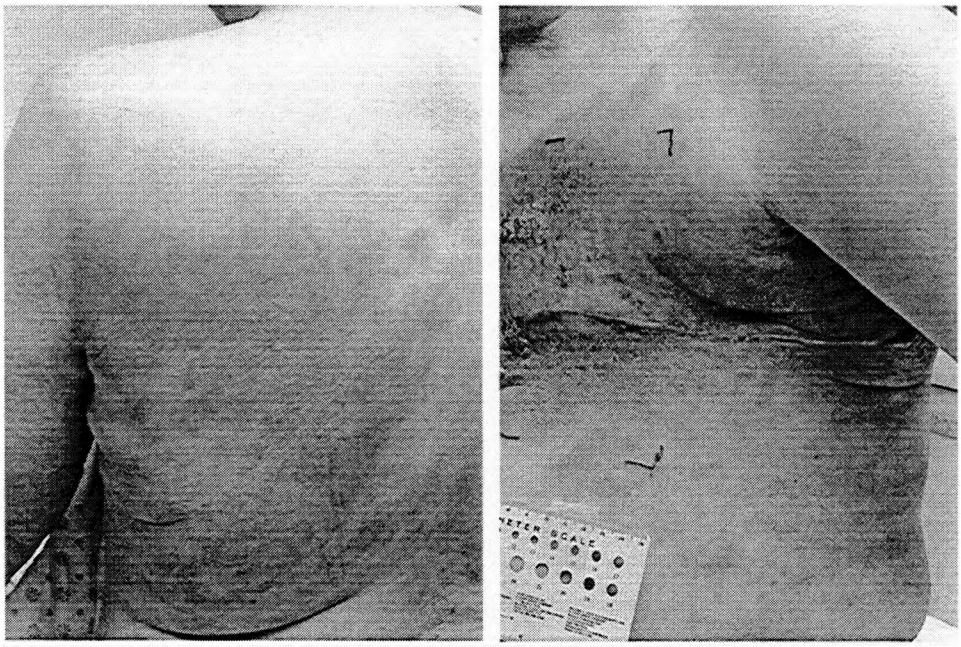


Fig. 1a - Two patients with diffuse chestwall recurrence of breast carcinoma, involving large areas of skin and superficial tissue to a depth of 5 - 7.5 mm.

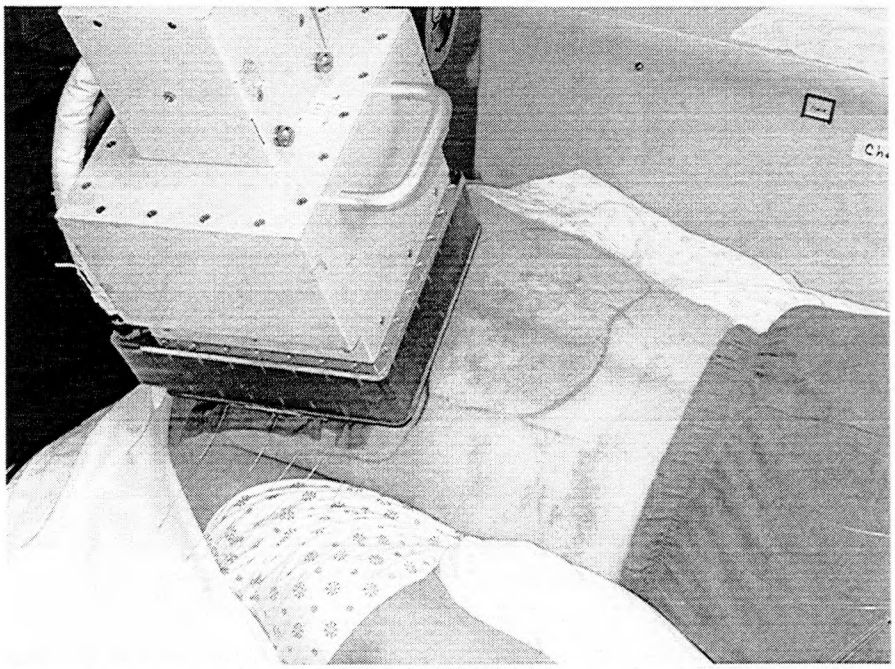


Fig. 1b - Patient with diffuse chestwall recurrence of breast carcinoma undergoing microwave hyperthermia treatment with a 16 element planar waveguide array applicator. Note the extensive superficial disease is broken into multiple treatment areas due to limited applicator treatment area.

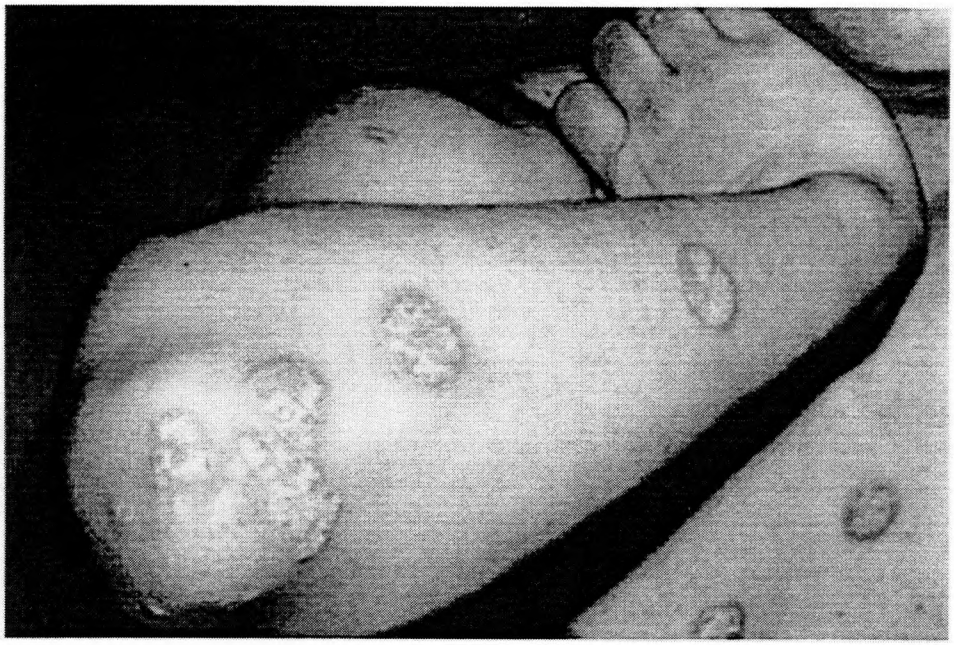


Fig. 2a - Case of "Mild Plaque Psoriasis" characterized by red patches on the skin, topped with a silvery, sloughing scale. Extent of disease varies considerably but is typically less than 3-5 mm in depth. Photo courtesy of the National Psoriasis Foundation.

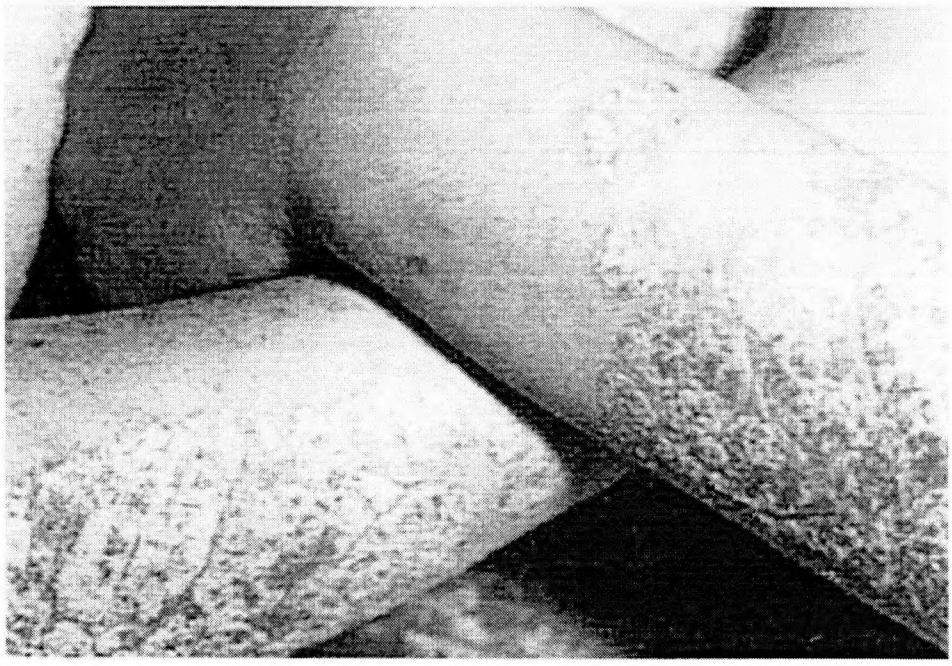


Fig. 2b - Case of "Moderate Plaque Psoriasis" characterized by red patches on the skin, topped with a heavy flaky scale. Photo courtesy of the National Psoriasis Foundation.

improvement in longevity of response or survival in patients with large area disease. It is important to note, however, that these encouraging initial results were obtained using first generation hyperthermia equipment, mostly with single channel microwave or ultrasound applicators that were incapable of adjusting their heating pattern to accommodate large or irregularly shaped tumors, or conforming closely to complex anatomic contours. Thus, subsequent application of these early hyperthermia systems to the treatment of larger and deeper tumors has met with increasing frustration. After years of study by the NCI-supported Hyperthermia Equipment Evaluation Contractors group [31-34] who contributed to the RTOG 81-04 randomized clinical trial [35], it was concluded that hyperthermia generated by single channel sources was incapable of producing adequate heating or significant improvement in response rates for tumors greater than about 3 cm across. Thus, in spite of impressive results for small tumors, the clinical application of hyperthermia to larger superficial tumors that are more likely to require adjuvant therapy (such as the typical range of chestwall recurrence cases shown in Fig.1) required the development of new more adaptable heating equipment to provide more uniform heating of larger surface areas spread over contoured regions of the body. These conclusions and the ensuing quest for equipment that could uniformly heat large surface areas overlying contoured anatomy spawned the development of numerous new hyperthermia applicator systems, as described in the following sections.

1.3 Goals of this Review

Though the title may suggest coverage of a large number of clinical applications ranging from cryotherapy and laser surgery removal of warts, moles, port wine stain, tattoos, etc., and moderate temperature acceleration of wound healing, these applications are actually beyond the scope of this review. Instead, this article will focus on the devices and techniques used to generate, monitor, and control moderate temperature thermal therapy or hyperthermia, which can be defined for this work as temperatures in the range of 41-45°C for 30-90 min, or $\leq$100 CEM43T_{90} [18]. Specific applications are for diseases of the skin and superficial tissues less than 2-3 cm deep for treatment of conditions like inflammation of the skin (psoriasis), and superficial cancers such as chestwall recurrence of breast carcinoma, metastatic melanoma, or superficially located tumor nodules of various histology. The intent is to summarize the major categories of devices that have been developed and used clinically over the past three decades and briefly differentiate the principles of operation and typical performance for representative equipment, with citations to the primary literature. No equations will be given nor detailed description of underlying physical principles. While an attempt has been made to describe representative examples of each significantly different technology, this article is not intended to be an exhaustive review of all available devices nor a complete listing of the relevant literature. The review is meant to supplement the more complete citations to the literature contained in each of the primary articles listed at the end of this section as well as previous excellent review articles and book chapters covering equipment and techniques for superficial hyperthermia by electromagnetic [36] and ultrasound [37, 38] techniques.

2. MECHANISMS OF HEATING

There are three primary mechanisms for heating biological tissue: 1) thermal conduction of heat flowing from a higher temperature source; 2) resistive (ohmic) or dielectric losses in tissue from an applied electromagnetic (EM) field; and 3) mechanical losses from molecular oscillations caused by an applied ultrasound (US) pressure wave. A few comments regarding the basic principles of each mechanism will be presented first. The underlying physical principles are described in the primary articles referenced below, in several excellent review articles, [39-42] and in books covering the field of hyperthermia in general [43-46].

2.1 Thermal conduction

The oldest and simplest technique for heating tissue is that of thermal conduction, normally applied either by total immersion of the desired body region (arm, leg, or entire body) in a temperature controlled air, water, or other heated fluid, by circulation of blood at higher temperature through the tissue, or by contact with a surface at elevated temperature. Due to efficient thermoregulation of the skin which exhibits up to 15 fold increase in vascular blood flow in response to excess heat [47], thermal convection cooling from well-distributed perfusion of 37°C blood is capable of maintaining very high thermal gradients and it is generally not possible to heat effectively more than 1-2 mm distance from a hot surface if the applied temperature is below pain and skin necrosing temperature thresholds [12, 43, 48]. Thus, thermal conduction is more often found useful for smoothing and regulating non-uniform temperature distributions induced by external power sources than as a sole mechanism of heating superficial skin disease.

2.2 Electromagnetic (EM) Power Deposition

All living tissues are comprised of electrical charges, some free and some bound. Tissues with high water content such as muscle, skin and body organs with good blood circulation have a high percentage of polar water molecules and thus conduct electrical current well. Tissues with low water content such as fat and bone have mostly bound charges that do not easily support conduction currents. Over the frequency range of interest for depositing power in tissue with non-ionizing radiation, all tissues may be considered as lossy dielectrics – somewhere between poor electrical conductors and poor insulators. The electrical properties of human tissues vary considerably from each other and as a function of frequency, and may be characterized by the relative dielectric constant (ε_r) and electrical conductivity (σ), as derived from the complex permitivity ε^*. The primary mechanism of EM heating of tissue also varies with frequency. At radiofrequencies below approximately 10 MHz, the alternating field induces a net movement of free electrons and power deposition results from "joule heating" or resistive (ohmic) losses associated with the induced current. At microwave frequencies above about 100 MHz, the radiative mode of electromagnetic propagation and dielectric losses in tissue predominate over the conduction current losses. Under these conditions, heating results primarily from friction caused by mechanical interactions between adjacent polar water molecules which are oscillating in an attempt to maintain alignment with the time varying electric field.

For both radiofrequency (RF) and microwave (MW) radiation, absorbed power density decreases exponentially with depth in tissue. In order to select the optimum frequency of EM field for applying energy to a specific tissue target, a number of factors

must be considered such as the target dimensions and proximity to adjacent critical normal tissues relative to the EM wavelength and desired penetration depth in tissue. A convenient compilation of parameters such as electrical conductivity, dielectric constant, and the wavelengths and penetration depths of electromagnetic waves in air, muscle and fat tissues is given in Fessenden and Hand [41]. For the practical range of frequencies used in hyperthermia from 1-1000 MHz, the wavelengths in soft tissue vary from about 4 cm at 1000 MHz up to 2 m at the lower RF frequencies. The maximum spatial resolution of power deposition is approximately one half this wavelength, or 2 cm – 1 m. As applicator size decreases relative to the wavelength, geometric beam divergence from the small aperture increasingly restricts penetration [49, 50]. The effective heating depth may decrease further as a result of power deposition peaks in the spatially complex antenna near field, and heterogeneities of tissue properties which increase reflection and refraction perturbations of the EM field at tissue interfaces. These later problems may be accommodated to some extent by appropriate applicator design and methods of coupling energy into the tissue volume. This has been the subject of significant research effort over the past two decades and has produced a variable degree of success at improving the localization and penetration of EM energy into the body, as described in the heating equipment section. Clearly, the upper microwave frequencies may be expected to provide localized heating of skin and superficially located tissues while the lower RF frequencies will affect large regions of the body.

2.3 Ultrasound (US) Power Deposition

Ultrasound energy propagates through tissue as a traveling pressure wave. Variations in pressure from the alternating compressive and expansive forces produce a physical displacement of tissue molecules in the direction of wave propagation. The absorption of vibrational energy in the molecules produces heat from mechanical losses. As a result of these losses, ultrasound energy within the pressure wave is attenuated as it propagates through tissue. Similar to EM radiation, ultrasound intensity decreases exponentially with distance into tissue with a tradeoff between effective localization of power superficially at the higher frequencies and deeper penetration due to decreased attenuation at the lower frequencies. Because the speed of sound (c_s) is orders of magnitude lower than the speed of light, the wavelength of ultrasound in tissue over the frequency range of interest (f = 0.5-10 MHz) is between λ = 0.1 and 3 mm. With wavelengths much shorter than the dimensions of both tumors and applicators, dispersion of the beam is minimal and well-collimated beams may be directed into very small volumes, unlike the much longer electromagnetic waves. Also because of the short wavelength, low frequency US sources may be used that provide penetration deep in the body. Tabulations of the acoustical properties of mammalian tissues and more detailed coverage of the physical interactions of ultrasound with tissue are available in a number of excellent reviews [38, 41, 51]

The primary parameters affecting the coupling of ultrasound energy into a given tumor volume at depth are the ultrasound source frequency, beam geometry, and tissue properties. Analogous to the near field diffraction effects seen with EM applicators, the pressure wavefront from an US transducer does not even approximate a monotonically decaying planewave until the far field. In clinical practice, the tumor volume almost always appears in the transducer near field instead, where there are spatially close fluctuations from minimum to maximum beam intensity [38]. Even with their spatially complex fields, ultrasound frequencies between 1.0 and 3.5 MHz are generally used for

external ultrasound hyperthermia applications due to their penetration depth characteristics. With intensity peaks and nulls only a few mm apart, secondary mechanisms such as reflections, scattering, and thermal conduction within the tissue are relied upon to smooth the resulting temperature distributions. For nonfocused applicators having no focal gain, effective tumor heating may be accomplished to a maximum depth of approximately 3-6 cm, usually using frequencies around 3.5 MHz [52]. Use of lower frequencies for large area superficial heating with non-focused US applicators generally produces increased pain due to unavoidable absorption in underlying bone. Deeper penetration is possible by focusing the US energy from a large surface area into a small focal region at depth and avoiding irradiation of all bone and air structures. Treatment of larger tumors may be accomplished by mechanically or electrically scanning the small focal volume around at depth to spread out the time averaged power deposition.

Another major factor effecting the coupling of ultrasound into the tumor is the presence of reflecting interfaces between the applicator and tumor. Minimizing perturbation of the US beam begins with appropriate preparation of the tissue surface to eliminate all air bubbles. Equally important is a continuous path of degassed temperature-controlled coupling water between applicator and skin. Appropriate bolusing techniques are described in the literature [52, 53]. Fortunately, the acoustic impedances of most soft tissues are quite similar so that once inside the skin there is little reflective loss during the propagation of ultrasound from one soft tissue to another. The impedances of bone, air, and lung are considerably different than those of soft tissues however, causing significant reflection and refraction of ultrasound energy at these interfaces. Almost complete reflection at soft tissue-gas interfaces and rapid absorption of the transmitted portion of the wave at soft tissue-bone interfaces often cause the most difficulty in using ultrasound clinically, especially for nonfocused beams directed into tissue overlying bone or air.

3. DEVICES & TECHNIQUES FOR HEATING SUPERFICIAL TISSUE

Over the past 25 years, countless devices have been investigated for improving the spatial and temporal control of energy deposition in biological tissue. Some developments have progressed through theoretical formulation only to die from lack of funding or missing critical technology. Other techniques that theoretically provide improved uniformity and control of SAR have not yet completed the prototype testing stage. Many devices have been built and used extensively at one or two institutions, but are not yet available to the hyperthermia community. Finally, the past two decades have produced a number of fully implemented devices that are available in commercial form. The net effect is that while important development efforts continue, there has already been significant improvement in the hardware and software available for clinical use today as compared to the equipment used in the multi-institution clinical trials of the 1980's [35, 54], and the 1990's [27]. Although the implementation varies considerably, the technologies and specific devices used for heating superficial tissue may be grouped together in the following general categories:

Electromagnetic

- Waveguide
  - Single or multiple aperture arrays
  - Phased or non-phased arrays
  - Stationary or robotically scanned
- Horns
  - Single or multiple aperture
  - Phased or non-phased arrays
- Microstrip Applicators
  - Single or multiple aperture
  - Single or multiple layer PCB
  - Planar or conformal
  - Spirals – Stationary or scanning
  - Dipole Surface Array – Stationary or scanning
  - Patches, annular slots, various geometry apertures
- Hybrid
  - Inductive loop "current sheet"
  - Multimode feeds "HEMA"
- RF Capacitive plate
- RF Dipole Feed Annular Phased Array
- Laser

Ultrasound

- Piston Transducer
  - Unfocused
  - Focused - convex shape or focusing lens
    - Lightly focused – no gain
    - Tightly focused – high gain
  - Stationary or robotically scanned
- Transducer Arrays
  - Planar or geometric focus
  - Stationary lightly focused transducers
  - Stationary lightly focused transducers - scanning reflector
  - Mechanically or electrically scanned transducers
    - Lightly focused transducer array
    - Focused transducer array

The following sections briefly describe the basic operating characteristics of about 25 different techniques for heating superficial tumors, as summarized in Table 1. These were selected from a much larger number of devices that have been researched over the past 20 years as representative of the range of techniques that have been used commonly in the past or are likely to prove useful for clinical hyperthermia in the near future. In light of ongoing development efforts, further significant improvements in the devices and techniques available for clinical hyperthermia are expected.

3.1 Electromagnetic Techniques.

The most basic electromagnetic applicator used for superficial hyperthermia has been the **microwave waveguide** with a single linearly polarized monopole feed [36, 55, 56]. Aperture size is designed with one side at least a half wavelength long in order to radiate a well-formed TE_{10} mode electric field oriented almost entirely tangential to skin-fat-muscle tissue interfaces to minimize overheating near tissue interfaces and high resistivity fat. In order to keep the rigid aperture dimensions small to fit closely to the desired target on contoured body surfaces, the interior of the waveguide is often filled or lined with high dielectric constant material to reduce the effective wavelength and thus aperture size. Such applicators are available from a number of commercial sources in a variety of sizes from 7.5 - 24 cm on a side, normally operated at about 430, 915 or 2450 MHz These waveguide applicators generally produce a roughly gaussian shaped beam distribution centered in the aperture front face with power deposition falling off to less than 50% of its peak before reaching the antenna perimeter laterally, or tissue depths greater than 1.5-2 cm [57, 58]. High dielectric constant temperature controlled coupling boluses are generally used between the waveguide and tissue surface to cool the skin, provide better impedance match of applicator to tissue, and smear SAR hot spots by reducing near field effects. Water ($\varepsilon_r = 80$) and mineral oil ($\varepsilon_r < 3$) are the most common bolus fluids and have been shown to significantly alter the power deposition patterns of direct coupled waveguide applicators, especially for non-homogenous bolus configurations [57]. The restricted lateral extent, rigid planar structure, and inflexible up/down power control of single aperture waveguide devices has in general limited their usefulness to small superficial tumors <3 cm diameter [35].

A number of approaches have been investigated to improve both the lateral extent and control of SAR distributions from single aperture waveguide applicators. One group increases the lateral extent of power deposition by placing a **variable absorption coupling bolus** in front of the aperture [59]. With a higher absorption saline pad under the central highest SAR portion of the waveguide, the multi-compartment coupling bolus provides reduced power deposition centrally and relatively higher SAR around the aperture periphery. For a typical commercial waveguide applicator, the authors report more than a doubling of area above 70% of maximum heating rate on the surface and at 1 cm depth in muscle phantom under the absorbing bolus pad [59]. A subsequent refinement of this bolus added another bolus layer consisting of a 5x5 grid of 3 cm square polyethylene bags which are connected individually to external saline filled syringes via 1.47 mm dia tubing [60]. This configuration allows spatial control of bolus attenuation by adjusting the amount of absorbing saline in each 3 cm square chamber. Both the central absorbing saline pad and the 25 saline pockets are immersed in temperature controlled distilled water coolant. In addition to providing spatial adjustability of SAR, the attenuating bolus was shown to provide up to a 46% increase in the lateral extent of the 70% SAR_{max} contour in phantom.

Another approach to modifying the SAR pattern of a single waveguide aperture has been to incorporate movable metal plate "vanes" within the aperture to form a convergent beam as it exits the waveguide [61-63]. Though minimum focal spot size and penetration are still constrained by the wavelength and tissue attenuation, a commercial implementation of this 430 MHz **Lens Applicator** has been used widely in Japan with good clinical success for tumors up to 3-5 cm depth [64]. Minimum, average and maximum

tumor temperatures of 40.7, 42.5, and 44.5°C, respectively, have been reported in one series of superficial tumors treated with the HTS-100 [65].

In order to treat larger superficial tumors, interest has shifted towards use of either robotically scanned antennas or multiple antenna arrays. Sterzer [66] was first to construct a **robotically scanned air coupled waveguide** applicator for heating larger areas of contoured anatomy. Tennant et. al. [67] added automatic feedback control to the scanning antenna system by mounting an infrared sensor on the scanning arm to non-invasively measure skin temperature just in front of the moving antenna. Subsequently, another group constructed a computer controlled motorized system for continuously rotating either one or two spiral microstrip antennas within a distilled water chamber over the target surface [68]. Using feedback signals from multiple temperature sensors located on the tissue surface and at depth, these **Scanning Spirals** produce good heating uniformity within regions much larger than the heating area of a single stationary spiral, with T_{min}, T_{ave}, and T_{max} intratumoral temperatures of 40.3, 42.6, and 44.9°C, respectively, reported for 1340 patient treatments of target areas up to 230 cm^2 with a scanning double spiral antenna at 433 MHz [69].

Alternatively, it is also logical to construct multi-aperture arrays in order to treat larger areas of superficial disease. Nilsson [70] described the heating patterns possible from a two aperture array of 10 x 10 cm waveguide applicators adjacent but angled at 30 or 45 degrees to each other and driven at either 200 or 434 MHz. This configuration, which mimics the treatment of intact breast tissue, was shown to provide either significantly increased penetration depth when driven coherently, or a spatially expanded superficial heating area from the tilted applicator pair with non-coherent fields. Fenn et. al. [71] describe a similar 915 MHz dual opposed waveguide pair for heating breast with the addition of implanted electric field probes and an adaptive phased array feedback control routine to optimize heating uniformity. Hand et al [72] discuss the theoretical improvement in lateral uniformity of SAR from a 4 x 4 array of 4 cm square (waveguide type) tangential electric field apertures as compared to a single 19 cm square aperture. Diederich and Stauffer [73] evaluated the first commercial device of this type, a 915 MHz 16 element **planar waveguide array**. They found this **Microtherm 1000** applicator suitable for treating superficial tissue regions up to 13 x 13 x 1.5 cm. Stauffer et al [74] reported a tight distribution of T_{90}, T_{50}, and T_{10} values (41.7, 42.5, and 43.4°C respectively) as averaged over the 60 min treatment intervals in the first 13 patients from stationary sensors at 203 intratumoral points and 483 points on the skin surface, and 40.8, 42.6, and 44.3°C, respectively, for 567 additional points mapped intratumorally (0.5-1.5 cm deep). The authors concluded that this water bag coupled planar array provides 50% iso-SAR coverage extending almost to the outer perimeter of the array for uniform heating of up to 169 cm^2 areas, while offering impressive adaptability of heating distribution to accommodate irregular tumor shapes [73]. Another array heating approach makes use of inductive loop coupled **Current Sheet Applicators (CSA)** which are smaller (7.3 x 5.9 x 3.3 cm) and lighter in weight than typical waveguide applicators and can be connected together in hinged flexible arrays for contoured surfaces [75-79]. Initial clinical results using 433 MHz four element CSA arrays for superficial chestwall disease have also demonstrated more uniform and higher overall temperature distributions than possible with earlier devices, with T_{min} and T_{ave} tumor temperatures of 41.0 ± 1.5°C and 42.2 ± 1.4°C, respectively obtained in the first patient series [80, 81].

Electromagnetic **horn applicators** are a close variant of the microwave waveguide, with tapered or flared openings to spread the radiated field from the waveguide base and to obtain better impedance match to the tissue load. In general, the horns provide somewhat larger effective field size than equivalent size waveguides with 50% SAR contours often extending outside of the aperture boundary in one direction. As with other applicators, the difficult challenge has been to obtain sufficient SAR between adjacent horns of an array. Lee [36] describes a commercial wideband **Dual Horn Applicator** that can be angled similar to the tilted waveguide approach of Nilsson [70], or mounted in parallel opposed positions and driven coherently in TEM mode to obtain deeper focused heating at frequencies as low as 87 MHz. Alternatively, the horns can be used individually and driven at 200-400 MHz for more superficial heating. Sells et al [82] describe the results of 1180 treatments of advanced or recurrent breast cancer with the single or dual horn configurations, showing good correlation of therapeutic response with number of heat treatments. Van Rhoon et al [83-85] describe a novel flared horn applicator with the two opposing metal sides that are parallel to the electric field replaced with low ε_r Lucite material to expand the SAR distribution in the H-plane. In addition, the authors replaced the distilled water loading of the conventional waveguide horn applicator with a central cone shaped wedge of low ε_r PVC material to further reduce SAR centrally and extend the peripheral heating characteristics of the applicator. The heating effectiveness of 1-6 element arrays of these **Lucite Cone Applicators (LCA)** has been compared to that of conventional horn arrays in matched clinical treatments [86]. The data demonstrate superior uniformity of heating from the new applicators with invasively measured temperatures averaging 0.28°C higher overall and 0.43°C higher peripherally. Due to improved heating around the applicator periphery, the LCA applicators are currently in routine use in Rotterdam in up to 3 x 2 arrays, treating surface areas up to 600 cm^2.

A hybrid approach has been developed by the group in Lille France which provides not only a novel **Microstrip-Microslot** heating aperture for superficial targets < 3 cm deep but also incorporates microwave radiometry capabilities within the same aperture for monitoring temperature during therapy [87]. This early paper presented results of the first 1000 treatments in 45 patients treated at either 434, 915, or 2450 MHz with a 4 cm diameter microstrip-microslot aperture using non-invasive temperature control by dual frequency 1 and 3 GHz radiometry. Subsequent efforts by this group have investigated larger 5 cm aperture **Multiapplicator** antennas [88, 89], multiple microstrip patch-slot applicators for larger heating area [90, 91], and enhanced dual frequency radiometry capabilities with software for calculating two dimensional thermal profiles during and after clinical hyperthermia treatments [92, 93].

In the past few years, considerable attention has been given to the use of printed circuit board (PCB) based **microstrip antenna** technology due to the ability to form almost arbitrarily large arrays from relatively low cost, lightweight and flexible PCB material. Several investigators have reported theoretical power deposition patterns possible with **microstrip patches** [94], **slot apertures** [95], and various configuration **spiral antennas** [96, 97]. These studies have demonstrated that a high normal electric field component exists immediately adjacent to microstrip radiators that falls off relative to the tangentially oriented field at increasing distance from the aperture, suggesting the use of thick water boluses to increase the tangential component of E field. Even with substantial bolus thickness, these applicators radiate complex E fields with a significant normal field component that will tend to reduce the penetration depth of effective

heating. Thus the use of microstrip applicators appears best suited to tumors that extend up to and include the tissue surface rather than those located beneath a layer of high resistivity normal tissue like fat. The largest single aperture microstrip applicator reported in the literature measures about 20 x 30 cm and can produce an effective field size ($\geq$ 50% SAR_{max}) of roughly 12.5 x 24 cm when driven at 434 MHz [98]. These **Contact Flexible Microstrip Applicators (CFMA)** are commercially available in several different sizes that can be used at frequencies ranging from 40 MHz to 915 MHz. The applicators have been shown to produce large effective field sizes up to 400 cm^2 with relatively uniform SAR patterns under the aperture perimeter in homogenous tissue phantoms [98, 99]. The applicators have been used extensively in clinical studies, though clinical thermal dosimetry and efficacy results have not been reported yet. While the applicators provide large effective heating area, concerns remain about the lack of adjustability of heating under a single feed applicator when placed over heterogeneous tissue. Another approach for large area heating is to incorporate an array of spiral microstrip antennas into a **Microwave Blanket** [96] which has up to 25 independently controlled heating elements (microstrip spirals) integrated into a 3 cm thick water bolus compartment for spatial smoothing of the radiated field. This conformable blanket concept appears well suited to treating superficial lesions like the typical cases shown in Fig. 1, as demonstrated by the large clinical experience of this group. Fessenden et. al. [69] reported successful use of the 25 aperture array for contoured anatomy up to 420 cm^2, with mean T_{min}, T_{ave} , and T_{max} intratumoral temperatures of 39.5, 41.9, and 44.4°C, respectively, in the first 356 treatments. Still, the 3 cm thick water bolus required for adequate divergence of the field peak centered under each spiral element substantially increases treatment setup complexity, power requirements, and hinders use of the array near complex anatomy. Ryan et. al. [97] investigated the use of multilayer **overlapping spirals** in order to provide more uniform power deposition between adjacent spirals using a thinner water bolus. He was successful in expanding the effectively heated area over that of a single spiral, but array size was not large for the number of antennas used due to the significant overlap required.

In summary, despite remarkable progress in the development of increasingly sophisticated scanning and stationary multi-element applicators, additional improvements are still needed to correct the awkward patient interface, to further expand the size, shape and adjustability of heating patterns, and to make effective, easy to use, and affordable devices available to the hyperthermia community. From previous clinical studies of hyperthermia for cancer therapy in patients with diffuse superficial disease such as the three patients shown in Fig. 1, and considering new applications of thermal therapy for skin disease such as the two patients shown in Fig. 2, the following design specifications for a superficial tissue (<1 cm deep) heating system seem appropriate:

Design Specifications for Large Area Superficial Hyperthermia Applicator

- Multiaperture array – Independently driven apertures for precise lateral adjustability
- Flexible - For highly contoured anatomy
- Low profile - Less bulky and awkward setup, allow simultaneous radiation
- Lightweight - For patient comfort and mobility during treatment
- Adjustable applicator for close fit to size, shape and location of target tissue
- Minimal setup complexity
- Low cost – Site and patient specific custom fitting applicators

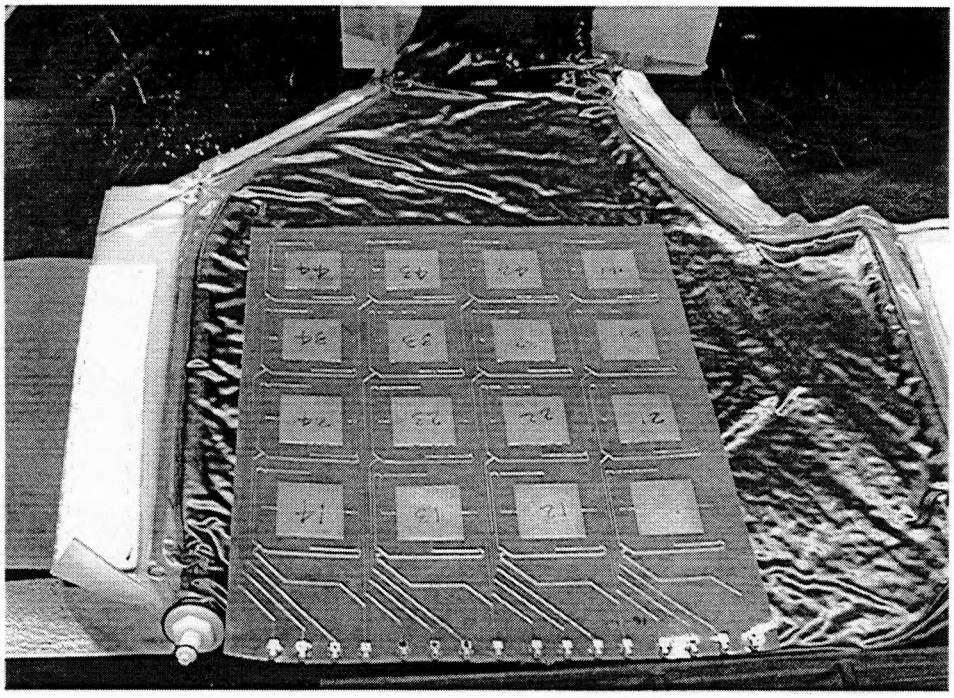


Fig. 3 - Photo of half-vest water bolus with elastic strap supports and back side of 16 aperture array of 4 cm square DCC apertures spaced 1.5 cm apart. Note the microstrip feedlines running from coaxial connectors at the PCB edge to symmetrically feed four sides of the back surface patches which couple to front surface patches or ring apertures.

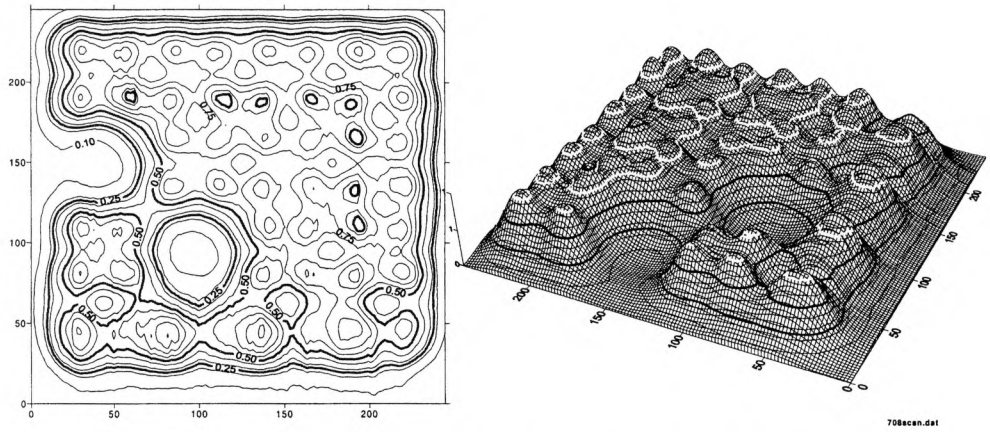


Fig. 4 - Measured relative SAR distribution 1 cm deep in muscle phantom from a 16 element array of 4 cm square DCC apertures spaced 1.5 cm apart, radiating through a 12 mm thick water bolus. Two apertures are off to demonstrate the resolution of power control of the antenna array. The two bold lines are 25% and 50% of SAR_{max}.

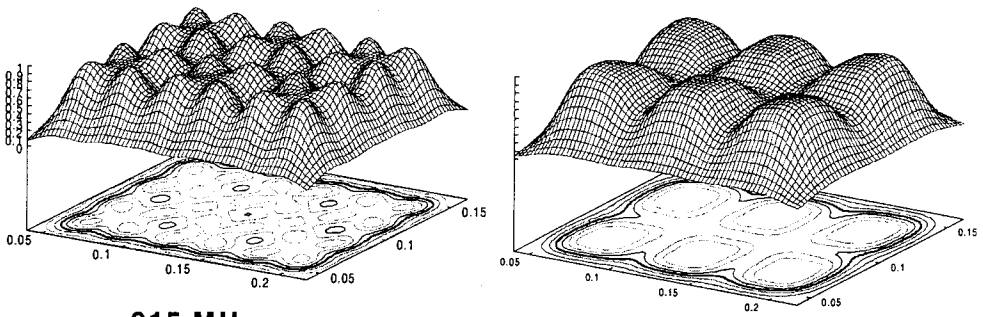


Fig. 5 - FDTD calculated SAR pattern 1 cm deep in muscle phantom under 6 element array of 4 cm square DCC apertures spaced 1.5 cm apart and coupled with 6.25 mm thick water bolus and driven at 915 or 433 MHz. Note that the bold contour, which represents 50% of SAR_{max} in the 1 cm deep plane, extends to the array perimeter demarcated by the dashed aperture outlines.

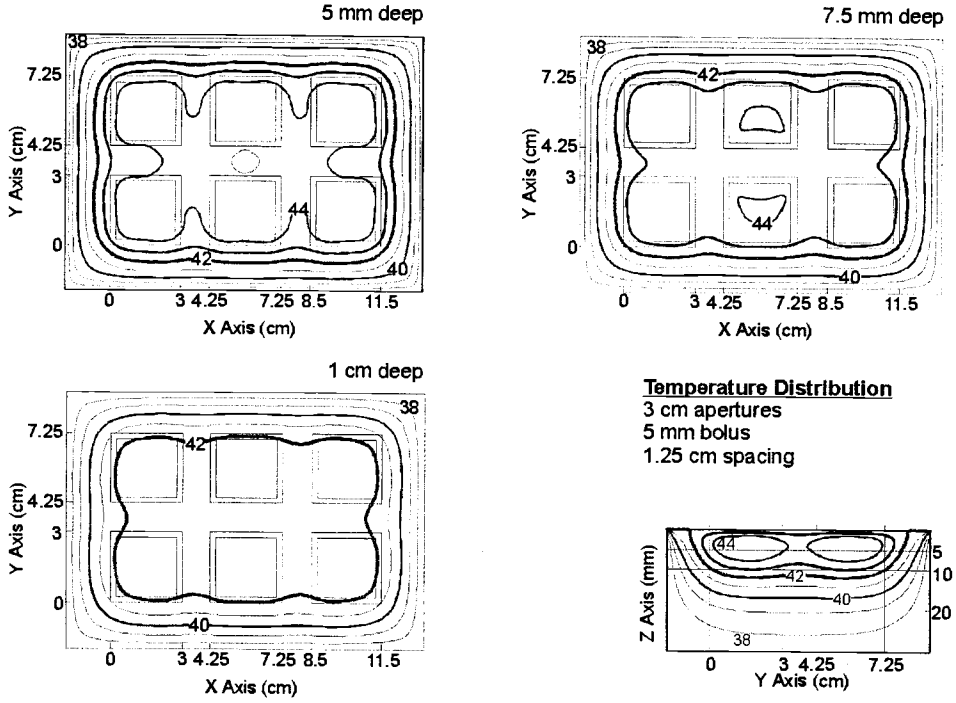


Fig. 6 - Temperature distribution predicted 5, 7.5 and 10 mm deep in muscle and central y-z cross section under 6 element array of 3 cm square DCC apertures coupled with 5 mm water bolus. Blood perfusion is assumed to be 2 kg/m^3s, water bolus temperature is 42°C and highest temperature point in tissue is 45°C. Note the 42°C contour in bold extends to the array perimeter down to 1 cm depth in muscle.

While many of the applicators described above fulfill at least some of these design specifications, none of the applicators available today provides a complete solution to the requirements for an effective large area heating device. This section looks at one example of a new system under development that should soon accommodate all of the above requirements. Stauffer et. al. [100] described the concept of a **Conformal Microwave Array (CMA)** applicator consisting of an array of square radiating apertures etched from a single layer of flexible copper foil and driven non-coherently at 915 MHz. Subsequently, radiation patterns from the constituent square annular slot **Dual Concentric Conductor (DCC)** apertures were analyzed theoretically with Finite Difference Time Domain (FDTD) simulations for a variety of aperture sizes and design configurations, and the simulations verified with experimental measurements of SAR in muscle equivalent phantoms [101-103]. Fig. 3 shows the back side microstrip feedline network of a 16 element CMA applicator lying on a 6.25 mm thick half-vest water bolus. In the clinic, this vest attaches with elastic and Velcro straps to cover the upper torso from mid-sternum around under the arm to mid-back. Fig. 4 shows the relative SAR pattern obtained in a plane 1 cm deep in muscle beneath the array of Fig. 3, with balanced 915 MHz power to 14 apertures and two apertures turned off to show the ability to restrict heating entirely under specific portions of the array when desired. For comparison, Fig. 5 shows the theoretical SAR pattern in a plane 1 cm deep in muscle for six 4 cm square apertures coupled with 6.25 mm water bolus. Note the characteristic four corner peaks in each square aperture at 915 MHz (left) which smooth out for the longer wavelength 433 MHz sources (right). The four corner peaks of each DCC aperture are also visible in the SAR scan of Fig. 4.

In an effort to predict SAR patterns from large conformal arrays in heterogeneous non-perfect loads, Rossetto and Stauffer [104] characterized SAR patterns for representative 6 element arrays placed over variable thickness water bolus (0.25-0.75 cm thickness), over rib sized bones lying 0.5 or 1 cm deep in muscle beneath 0 or 0.5 cm layers of fat, and for the array heating through a 0.5 cm water bolus with various size pockets of air trapped between the water bolus and skin surface. Several important conclusions were reached which may have significance for other microwave applicators as well. First, neither the presence of ribs close to the skin surface nor variations of up to a factor of three in water bolus thickness restricted use of 915 MHz DCC aperture arrays for superficial tissue heating. Secondly, the presence of even small air bubbles can significantly alter the power deposition pattern from the microwave radiators, depending on bubble size and location under the array, suggesting a benefit from careful preparation of the coupling bolus. While alarming, this later conclusion is not unexpected in light of other investigators who have shown as high as 20% perturbation from low ε_r temperature probe catheters in microwave fields [105]. Although thermal conduction and convection effects in tissue will tend to smooth out the temperature distribution which results from the perturbed SAR pattern, this study re-emphasizes the importance of minimizing air in the path of high dielectric (water) coupled microwave apertures regardless of design. In subsequent work, Rossetto et. al. [106] used a BioHeat equation based Finite Difference program to convert the FDTD calculated SAR patterns to steady state thermal distributions for a variety of tissue blood perfusion conditions, in order to optimize array design parameters such as spacing between apertures and bolus thickness for DCC apertures ranging in size from 2.5 to 4 cm square. Fig. 6 shows the thermal distribution expected in planes 5, 7.5 and 10 mm deep in muscle under a 6 element array of 3 cm square DCC apertures spaced 1.5 cm apart. As discussed in that work for the simulated

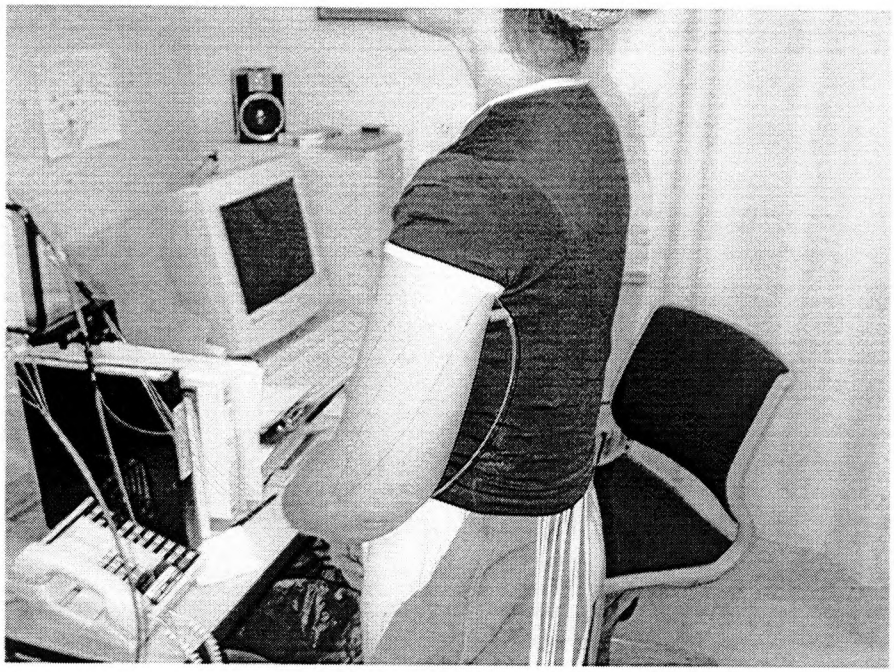
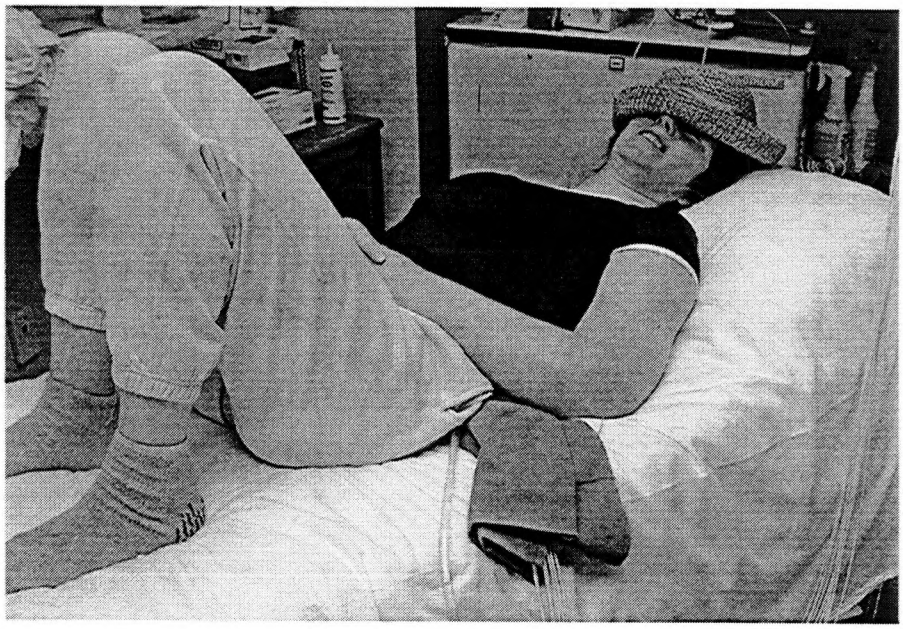


Fig. 7 – Photo of patient with diffuse chestwall disease undergoing hyperthermia treatment with Conformal Microwave Array applicator on 6.25 mm water bolus vest underneath a stretchable fabric overshirt. Note the 16 coax cable feedlines and two water tube connections exiting under the shirt, and 4 fiberoptic temperature probes which enter through the sleeve and extend along the tissue surface 20 cm across each row of apertures for temperature mapping during the heat treatment in either standing (above), sitting (not shown), or prone (below) positions.



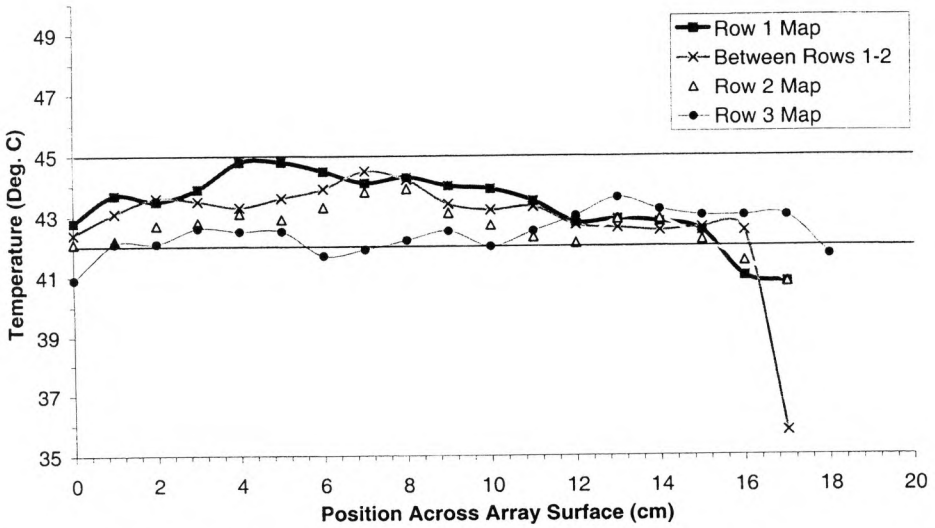


Fig. 8 - Steady state temperatures obtained during clinical hyperthermia treatment of chestwall recurrence of breast carcinoma spread across 20x40 cm region of a patient's back. Temperatures were measured on the skin surface under a 16 x 16 cm CMA applicator coupled with 6.25 mm water bolus at 42.5°C – during the treatment of Fig. 7.

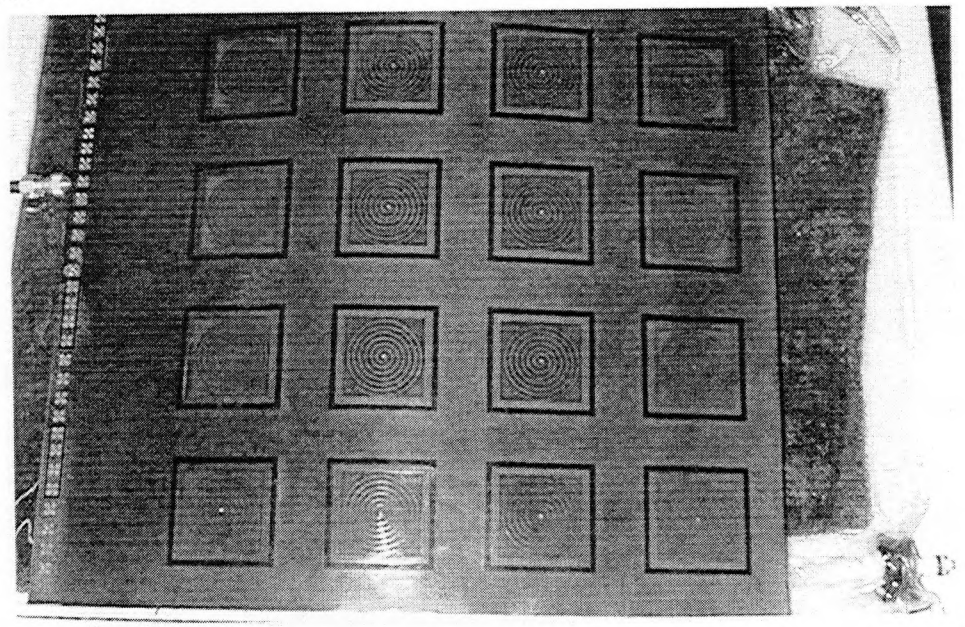


Fig. 9 – Photograph of 3 layer PCB Dual Mode conformal array applicator with spiral receive mode antennas for radiometry located concentrically inside 4 cm square Dual Concentric Conductor (DCC) heating apertures. Excitation of the DCC inner conducting rims is provided by a microstrip feedline network in the middle copper layer and microstrip feedlines from a second set of coax connectors run in the back copper layer to the central spiral antennas..

conditions of 42°C water bolus and 45°C peak temperature in moderately perfused tissue, the 42°C contour line (bold) is in close agreement with the 50% SAR contour and extends out to the array perimeter to a depth of 1 cm.

For practical use of the applicators, the large 16 and 32 element flexible PCB arrays are integrated together with a 0.6-1.2 cm thick water bolus vest, jacket or blanket that fits tightly against the patient [107]. With an elastic wrap or overshirt to attach the Conformal Microwave Array applicator to the patient surface, initial clinical studies have demonstrated the capability of treating extensive skin disease covering for instance most of the back, with the patient either sitting in a chair, lying on a bed, or standing and pacing during treatment (Fig. 7). In addition, because the 0.005-0.010" PCB is essentially radiation transparent, external radiation may be delivered simultaneously with microwave heating if desired for maximum synergism of treatments. Initial reports of preliminary clinical experiences with these large area applicators describe improved patient comfort due to the lightweight and flexible structure and significantly improved patient tolerance due to the ability to shift positions during treatment without interrupting power. Studies with an early prototype CMA applicator produced temperatures ranging from 41.5-44.8°C in all thermally mapped points on the surface and at 0.5-1 cm depth under the tumor [108]. Recent larger CMA applicators with integrated microstrip feedlines and custom fabricated water bolus vests have provided a similar range of temperatures (42-45°C) as determined by thermal maps of over 70 skin temperatures under a 16 x 16 cm applicator [108]. See Fig. 8. As the CMA applicators expand in size from the 16 element arrays described above to the current capability of 32 individually controllable apertures, the requirement for rapid thermal mapping of temperatures under the array becomes even more stringent in order to take advantage of the spatial adjustability of SAR. Current efforts are focused on adding microwave radiometry measurement of tissue temperature under each individually powered aperture by monitoring the received signals from a second set of 32 spiral antennas located one in the center of each DCC heating aperture [107]. A prototype three layer PCB dual mode CMA applicator with concentric DCC and spiral antenna elements for radiometrically controlled heating is shown in Fig. 9.

A listing of common electromagnetic applicators used in the large clinical studies of the 1980's and their treatment capabilities is given in Table 2 along with comparable results for several more recent array applicators. Note the improvement in percentage of aperture face area that is covered by the $\geq$ 50% SAR contour in the more recent devices. For applicators with close to 100% aperture face $\geq$ 50% SAR, well-controlled effective heating of the entire area under the applicator should be possible.

3.2 Ultrasound Techniques.

Early efforts to apply ultrasound for superficial heating applications used single round disk planar **piston transducers** operating at 0.5-3.5 MHz, normally coupled to the skin with a short 5-20 cm column of degassed water which also served to cool the vibrating transducer and skin surface [109-111]. The combination of only up/down power control with no ability to shape or steer the centrally peaked power deposition pattern under the aperture restricted clinical applicability of these devices to small superficial lesions. One approach used to increase the heating area of single planar ultrasound applicators is to introduce a non-vibrating section in the center of the transducer [112].

More recently, multi-element array devices have been constructed to increase the lateral extent and control of heating. The **Sonotherm 1000** is one such device with 16 individually controllable transducers arranged in a 15 cm square 4 x 4 **unfocussed planar array** that is coupled to the patient with an attached 6-8 cm thick floppy bag of degassed water [113-115]. Because of its extremely well-collimated beam [37, 116], this stationary non-focused array has been used successfully for a variety of superficial tumors up to 225 cm^2 across and less than 4-6 cm or occasionally up to 8 cm deep in the neck, thorax, trunk, and extremities [52]. For smaller area tumors, a 7.5 cm square 2 x 2 element planar array applicator is also available with nearly identical heating characteristics except one quarter the surface area for heating in tight spaces such as neck, axilla, and groin. For either array, two frequencies are available (1.0 and 3.5 MHz). While 1.0 MHz provides deeper penetration for tumors extending 6-8 cm deep, use of lower frequencies with unfocussed transducers often increases problems with patient pain during treatment. The higher frequency of 3.5 MHz is generally more tolerable for the patient and provides effective heating to approximately 3 cm depth.

Other approaches have sought to take advantage of the precise focusing and deep penetration capabilities of ultrasound by using arrays of tightly focused transducers aimed to a common focal spot at depth. Initial systems used a small number of low frequency transducers (1 MHz) producing a small focal spot at depth which was mechanically scanned rapidly around the tumor to paint a larger temporally averaged heating pattern [117, 118]. In principle, when scanning a small high intensity region, the effect of intensity gain at the focal spot compared to that on the tissue surface is diminished directly in proportion to the area scanned. Increasing the scan area for larger tumors reduces time-averaged power absorption at depth so that system power, and corresponding SAR in surface tissues within the US entrance window, are increased proportionally, providing an upper limit on treatment volume at depth. This has not been a significant limitation as **Scanned Focused Ultrasound (SFUS)** has been used successfully in the clinic for a variety of superficial and moderate depth tumors including those in the breast, lower abdomen, pelvis, and even head and neck tumors including brain (via craniectomy). Time-averaged tumor T_{min} and T_{max} temperatures of 39.6 ± 1.5°C and 44.0 ± 2.4°C were reported for the first 160 treatments by one group [119] quite similar to the clinical experience of an independent group testing the **Sonotherm 6500**, a commercial implementation of the original University-developed system [120]. Continued development, including the addition of higher frequency transducers (4 MHz) and a patient pain feedback button, have extended the usefulness of this scanning ultrasound technique to skin and superficial targets up to 20 x 20 cm x 3-4 cm depth. Significantly improved spatial control of power deposition has been reported due to computer control of operating frequency and applied power levels as a function of scan position, taking into account tissue geometry and patient pain response, with the net effect of increasing average minimum and maximum tumor temperatures from this SFUS system to 41.1±1.1°C and 45.9±2.7°C [121].

Rather than mechanically scanning an array of transducers, Lu et. al. [122] developed a large (25 cm ID) **Cylindrical Array** with 8 stacked rings of stationary transducers all directed inwards for treatment of intact breast. In practice, the array mounts under a hole in a table upon which the patient lies prone during treatment. Each ring consists of up to 48 transducers alternating between either high (4.3-4.8 MHz) or low frequency (1.8-2.8 MHz). By careful mixing of high and low frequency transducers and

adjustment of relative power and phase to the transducer elements, this geometrically focused array is shown theoretically capable of selective heating of predominantly superficial tissue, one quadrant, or the entire breast. Other methods of electronically phase focusing and steering without mechanical movement of large arrays include the **Sector-Vortex** [123, 124], **Cylindrical Section Array** [125], and **Spherical Section Array** [126, 127] applicators, which generally require a large number of power sources as well as sophisticated phase and amplitude control techniques. Another method of generating complex beam patterns such as simultaneous multiple foci power deposition from a stationary source is using **Field Conjugate Acoustic Lens** applicators as described by Lalonde and Hunt [128].

While most of the above ultrasound techniques were developed primarily for heating small to moderate size tumor nodules located at some depth in tissue, Moros et. al. [129, 130] describe **a Scanning Ultrasound Reflector Linear Array System (SURLAS)** for heating superficial targers by moving a wedge or triangular shaped acoustic reflector back and forth across the target tissue within a thin waterfilled rectangular structure that is sealed to the body surface. Heating is provided by a 1 x 4 element planar array of ultrasound transducers at one or both ends of the scan box aimed across the target surface toward the moving reflector. A subsequent refinement included a 5.0 MHz array of transducers at one end as well as the 1.0 MHz array at the opposite end [131]. By dynamic computer control of both the power and percentage of high and low frequency insonication as a function of position over the target, the penetration depth of effective heating can be varied from superficial to deep during the scan. This system provides not only the capability of heating up to about 100 cm^2 areas of superficial tissue, but also has no radiation perturbing objects above the target so that external beam radiation can be delivered simultaneously with the ultrasound heat if desired for maximum synergism of treatments. Future scanning reflector systems may be enlarged to the point where scan cycle times exceed 10-20 sec where temporal fluctuations of temperature become significant.

3.3 Regional Heating Techniques of Potential Use

The most common regional heating approaches involve the use of radiated EM fields in the frequency range of 10-100 MHz where the wavelength in tissue is large, approaching the height of the human body in many cases, and thus controlled focusing of heat into a small portion of the torso is not possible. These techniques are intended to heat a large region which includes the tumor, and rely on significantly different local tumor characteristics (such as lower blood perfusion or higher electrical conductivity) to provide localization of temperature rise. In general, the EM regional heating approaches may be characterized as producing moderate temperatures (39-42°C) within the tumor target, while usually limited by unavoidable power deposition in adjacent normal tissues.

Perhaps the most basic single channel device that has seen extensive clinical application in Japan is the use of **Radiofrequency Capacitive Heating** devices driven at frequencies between 8 and 27 MHz, such as the **Thermotron Rf-8** [132]. This device creates an electric field between two saline bolus-coupled metal plate electrodes which are placed on opposite sides of the patient. With this configuration, the conduction currents are coupled capacitively through the electrode bolus into the patient and may be concentrated under the electrode with smaller diameter. While Kato et. al. [133] suggest

that heating of large superficial tissue regions is not recommended, Lee et. al. [134] report moderate success with modest temperatures achieved in 22 patients with chestwall disease (T_{max}= 41.9, T_{ave} = 41.1, and T_{min}=39.9°C).

It is possible to heat at depth in the body by using a low penetrating frequency and an array of radiating apertures that are appropriately phased so the individual fields add constructively in the target. The first commercial device built for this approach was the **Annular Phased Array (APAS)** which consisted of an array of 8 equal power, equal phase radiators mounted on the surface of a large cylinder which was coupled tightly around the body torso with a refillable distilled water bolus [135]. Subsequent development of the 60-120 MHz **Sigma 60** applicator increased control flexibility via four independent relative phase and amplitude controls for the 8 dipoles as well as improved the patient interface. The usefulness of this device has been expanded with CT scan based 3-D treatment planning [136], phase optimization algorithms for real-time E-field focusing in tumor and nulling in critical normal tissues using feedback from multiple E-field probes [137], and recently by hardware improvements which produced the **Sigma Eye** applicator with 12 individually controllable dipoles (amplitude and phase) and integral MRI scanner for realtime planning and treatment monitoring [138]. While this device is primarily intended for heating deep seated tumors, it has been used for widespread superficial heating in some patients [139].

A variety of other EM radiating devices have been developed and tested at only one or two hyperthermia centers but show promise. One group in Amsterdam has constructed a system with four large independently positioned 70 MHz waveguide sources to provide flexibility of anatomic positioning as well as phase and amplitude steering of power deposition in the body [140]. This four waveguide array or **Matched Phased Array (MPA)** system has been used in clinical studies of deep heating in the pelvis since 1987, with the investigators reporting moderate temperatures (40-41°C) in deep seated tumors of most patients, and >42°C temperatures in only 27% of patients [141]. Several more groups are investigating new techniques for concentrating RF energy in a local region at depth by superposition of EM waves from two or more inductively or capacitively coupled applicators [142-147]. These combined field approaches are intended to provide focusing of energy at depth as a result of constructive interference patterns between multiple fields. In most cases, these applicators can be adjusted to provide some control over superficial heating as well, though the predominant application for these devices has been for deep sites.

4. THERMOMETRY AND QUALITY ASSURANCE

Appropriate monitoring of tissue temperature during clinical hyperthermia is an essential component of therapy. While thermal dose is still not defined precisely, important correlations between thermal isoeffect dose expressed as Cumulative Equivalent Minutes at 43°C (CEM 43°) and tumor response have begun to emerge from carefully analyzed clinical studies [18, 24, 148]. Improved analyses for future clinical trials will require more complete knowledge of the tumor temperature distributions which in general have been only sparsely sampled in previous clinical trials. The most commonly used techniques for monitoring tissue temperature during clinical hyperthermia are identified below. The physical principles underlying the thermometry hardware and

thermal dosimetry techniques have been presented innumerable times in the literature, and are summarized in the following reviews [46, 149, 150].

4.1 Non-Invasive Thermometry Techniques

While the vast majority of thermal dosimetry for hyperthermia has been performed using invasive temperature probes to sample a small number of points, there are a number of non-invasive approaches under investigation which can quantify more complete 2-D and 3-D temperature distributions. **Infrared Thermography** is well suited to the measurement of large surface temperature distributions, but practical considerations have restricted its usefulness primarily to the dosimetry of SAR patterns in split-phantom models [151, 152]. Tennant et. al. [67] have described a clinically useful technique of reading 2D skin temperatures with a narrow beam infrared camera aimed just in front of a scanning microwave antenna for use in feedback control of antenna power level. Temperature dependent signals in tissue have also been quantified using **Computerized Axial Tomography** [153] and **Ultrasound Time Of Flight Tomography** [154] techniques, though recent ultrasound research has focused on a more sensitive technique involving signal processing of the back scattered signal of standard diagnostic US images [155, 156]. Using a pulse echo diagnostic ultrasound imager, an accuracy of better than 0.5°C and spatial resolution of 2 mm has been obtained in phantom [156]. **Applied Potential Tomography (APT)**, sometimes called **Electrical Impedance Tomography (EIT)**, is performed by measuring tissue impedances between multiplexed pairs of electrodes within a circular array around the target tissue. Usable spatial resolutions of about 10% of the electrode array diameter (1-3 cm) and about 0.3°C have been obtained in phantom studies [157, 158], and software enhancements are currently underway to improve resolution and accuracy in the more challenging heterogeneous tissue environment using interstitial electrodes in addition to surface electrodes.

Similarly, MW antennas can be used not only for depositing energy, but also as sensitive receivers to collect temperature-dependent blackbody radiation from nearby tissues. With a direct tradeoff between sense volume and spatial resolution determined by the wavelength, multi-frequency **Microwave Radiometry** appears most useful for combined heating and monitoring of superficial tissues, or deep tissues that are implanted with closely spaced arrays of interstitial MW antennas. Very promising initial results have been obtained with dual-frequency radiometers multiplexed within an array of implanted antennas for radiometry controlled interstitial heating at 915 MHz [159] and coupled to external microwave antennas for monitoring and control of superficial heating [87, 160]. By taking advantage of the different sense volume of radiometer antennas at different frequencies, Mizushina et al [161-163] have described up to 5 band radiometry techniques capable of discriminating the profile of temperature with depth in tissue to a maximum depth of about 4.5 cm. Others are looking at a computed **Microwave Tomography** approach using a closely spaced array of microwave antennas where each antenna is pulsed one at a time in sequence around the array while recording received energy at all other antenna positions [164, 165]. Chang et. al. [166] describe an active imaging system with 14.75 cm diameter array of 16 antennas operating over 300-900 MHz band and producing a maximum temperature precision of 0.98°C and relative accuracy of 0.56°C.

While difficulties resulting from heterogeneous tissue properties remain to be solved, realtime multi-slice **Magnetic Resonance Imaging** is already a practical and extremely

useful technique for non-invasive monitoring of tissue temperature and physiologic changes during heat therapy [167-172]. Current efforts have demonstrated resolutions on the order of 0.5°C in 1 cm^3 sense regions with scan acquisition times of less than 1 min and have been used to monitor and control non-invasive thermal therapy. By combining information with invasively sampled temperatures, the non-invasively measured distributions should provide essential validation of thermal model based treatment planning which should lead to improved treatment control and higher, more uniform thermal doses.

4.2 Invasive Thermometry Techniques

Thermocouples are one of the primary monitoring techniques for clinical hyperthermia due to their low cost and simple operation. Commercially available probes may be used interchangeably with an accuracy of ±0.2-0.3°C which is stable over many years. Because of the high thermal conductivity of copper, the most Common **Copper-Constantan Thermocouple Probes** produce significant (>2°C) thermal conduction smearing of high thermal gradients [173, 174], so that many users have switched recently to electrically similar **Manganin-Constantan Thermocouples** with lower conductivity and smearing errors [175]. While commercial readout systems designed specifically for manganin probes are not yet available, most copper-constantan systems are easily recalibrated to yield an accuracy of ±0.3°C over a restricted range of 35-55°C [176], which is a definite improvement over the alternative thermal smearing errors of copper based probes. While miniature bare wire probes are best, fused silica tubing or metal needle encased thermocouples work well for thermometry in ultrasound fields to reduce self-heating and field perturbation effects. With appropriate filtering, shielding, and arranging wires perpendicular to the electric field, thermocouples have been used successfully in RF fields but are generally not recommended for microwave thermometry [105, 177, 178]. Instead, **Fiberoptic Probes** consisting of plastic or glass fibers with a non-metallic temperature sensing elements at 1-7 locations along the fibers have proven more capable of minimizing reading artifacts and field perturbations. Current systems provide essentially artifact free readout of temperature even in the most intense EM fields but are prone to drifting (0.5-1°C per day) and must be recalibrated prior to each heat treatment to maintain accuracy within ±0.3°C over a 2-3 hour interval. The fragile probes are generally inserted through soft plastic catheters which may be left in the tumor between treatments with excellent patient tolerance. While the lossy plastic probes are generally not recommended for US dosimetry, fiberoptics have proven useful for accurate thermal mapping of US irradiated tissues when inserted inside small diameter metal needles to minimize probe self-heating [179]. Following careful multipoint temperature calibration, **High Resistance Lead Thermistors** exhibit very good accuracy and precision, and longer term stability than fiberoptic sensors. Similar to fiberoptics, the probes have excellent immunity to electrical readout artifacts and calibration is unique to each sensor so probes are not interchangeable. These probes are generally not recommended for ultrasound thermometry due to self-heating artifacts and perturbation of the US field from the carbon impregnated plastic leads. Several other probe technologies are under development including a special purpose **Miniature Thermistor Chip Array** for US thermometry, and a multipurpose **Thermal Diffusion Probe** capable of measuring temperature, thermal conductivity, and effective tissue perfusion by alternately applying transient heat pulses and passively monitoring temperature from an array of miniature silicone wafer CMOS technology beads located along either a plastic catheter or steel needle probe [180]. Alternatively, rather than monitor the slowly changing tissue

temperature response to applied power, probes and software are evolving for direct measurement and rapid maximizing or minimizing of electric field [181] or ultrasound intensity [182].

3.3 Potential Sources of Error in Clinical Invasive Thermometry

Thermometry of clinical hyperthermia treatments must be performed with great care to minimize errors associated with interactions between the heating field, probes, and readout electronics. Optimum techniques for measuring temperature in EM fields differ from those required for US dosimetry. For **Electromagnetic Heating** approaches, there are three unique sources of measurement error that must be minimized Probe Self-heating due to electrical currents induced in any electrically conducting material, Electromagnetic Interference (EMI) pickup in the readout electronics, and EM Field Perturbation due to the presence of a probe. In general, these errors may be minimized by using probes with no conducting metal, EMI filtering/shielding of the readout device, minimizing probe size, and orienting probes perpendicular to the field [105, 177, 178, 183]. For the **Ultrasound Heating** approaches, temperature readout errors occur primarily as a result of Probe Self-Heating due to absorption of US energy in soft plastics. Teflon coatings commonly used for insulating thermocouple wires are particularly bad, as are fiberoptic and most soft plastic catheter materials. The sensors are usually encased in metal to minimize absorption heating, although this increases the viscous heating artifact from shear forces between tissue fluids and metal surfaces if the probes are not small compared to the US wavelength (0.25-1.5 mm). Minimization of Field Perturbation, or distortion of the propagating ultrasound wave, also requires use of probes that are small compared to the wavelength to avoid hot and cold spots in tissue from reflections off the probe surface and shadowing of tissues behind the probe. For highly focused scanning US beams, the intense fields require special monitoring techniques, including scanning the beam around the sensors, turning power off as the beam scans over the sensors, and using specially shielded implant catheters [184].

For accurate thermometry of clinical hyperthermia treatments, care must be taken to minimize several additional errors that can occur with any heating modality. Probes constructed with high thermal conductivity materials (eg. copper wire) can produce **thermal conduction smearing** errors of ±2°C or more, depending on thermal gradient and probe size [173, 185]. Methods of reducing this error include minimizing the number and size of wires and replacing all copper with lower thermal conductivity materials like Manganin/Constantan, Chromel/Alumel, or preferably non-metallic optical fibers. **Uncertainty of sensor position** within the probe is another potential source of error, especially in soft plastic sheathed probes which are susceptible to stretching so that sensor locations may shift proximally from the tip as the probe ages. Typical fiberoptic probes may have between 2 and 10 mm of space beyond the most distal sensor even though they are marked as having "tip" sensors. Longitudinal uncertainty of sensor location is almost entirely avoidable with proper QA, which should be performed periodically on all probes including metal needle probes [186]. **Response time**, or the time to reach 95% of final reading, varies from <0.1 sec for bare wire thermocouples to >1-2 sec for fiberoptic probes. The effective response time under certain clinical conditions can increase to 10 sec or more however. These potential errors may be minimized by using appropriate data acquisition intervals, minimizing probe and catheter size, aligning probes perpendicular to the propagating field, and if necessary inserting mineral oil or

water in the catheter to increase thermal conduction between the catheter wall and sensors.

4.4 Probe Placement Considerations

While early hyperthermia trials generally used 1-8 temperature sensors in predominantly fixed positions, more recent studies generally report a much larger number of temperatures recorded from "thermal maps" or linear profiles of temperature measured at 0.25-1 cm spaced increments along catheters located both at depth in tumor and on the skin surface. These 1-D temperature profiles are obtained via automated thermal mapping systems that scan probes repetitively during treatment [187] or from manually mapped single or multiple sensor probes. Thermometry guidelines published for the RTOG trials of hyperthermia recommended that temperatures be mapped along each probe track at least once every 10 minutes, in increments of no more than 5 mm for tumors < 5 cm and 1 cm for tumors >5 cm across [188]. Additional quality assurance guidelines specific to ultrasound heating [186, 189, 190] provide guidance for recommended placement of thermometry sensors and documentation of treatment parameters. As summarized in a recent review [191], these guidelines specify the number of implanted catheters required as a function of lesion size and present implant strategies to ensure monitoring of minimum and maximum temperatures in tumor and surrounding normal tissues. While most clinical situations are covered adequately in these guidelines, appropriate procedures for thermometry will continue to evolve. Already, new equipment-specific temperature control routines have been reported for large multi-element applicators [192] and scanning high intensity ultrasound [193]. Future heating systems are likely to provide computer calculated 2D and 3D temperature distributions in addition to the measured data, obtained via real-time thermal modeling interpolation of tissue temperature between measured points [194], or from non-invasive monitoring of thermal distributions.

5. SUMMARY – EQUIPMENT FOR HYPERTHERMIA

We are in a continuing phase of rapid evolution in the devices and techniques available for heat treatment of skin and superficial tissue disease. Developments of the past two decades have led to significant improvement in the size of target volume that can be heated, in the degree of control over heating, and consequently in the uniformity of heating and number of sites that can be addressed. The most significant advances in Electromagnetic heating technology include the move from single planar aperture sources towards much larger multiaperture conformal arrays with adjustable SAR patterns, from air cooling or fixed temperature coupling of skin to precise temperature-regulated custom fitting water bolus "pads", from 1-8 fixed point temperature measurements to either thermal mapping with 100 or more points or non-invasively monitored 2D and 3D temperature distributions. The most significant advances in Ultrasound heating technology include the move from single to multiple transducer arrays, from stationary to mechanically or electrically scanned transducers, from single frequency to dynamic realtime frequency modulation, from 1-8 fixed point temperature monitoring to feedback control from non-invasive realtime characterization of temperature and physiologic changes during treatment. The net effect of all these developments is that although current technology can provide significantly improved thermal therapy over earlier systems, our work is far from done. Additional developments are necessary to further

customize applicators for many sites and the commercial sector has been slow to finalize product design and actively market the newer technologies, due in large part to lackluster clinical demand for heating equipment spawned by years of frustration with inadequately controlled first generation devices.

Proper selection of heating equipment for a particular application will depend on the tumor site, size and proximity to critical normal tissues, and desired target temperature. Electromagnetic sources can provide either deep penetration of a regional heating field at low RF frequencies (0.1-200 MHz), or can be localized to tumor-sized volumes within 1-3 cm of the tissue surface at microwave frequencies above 200-400 MHz. Large multi-aperture arrays of non-coherent MW antennas seem most effective for heating diffuse shallow depth diseases such as psoriasis and chestwall recurrence of breast carcinoma. Multi-element arrays of non-focused ultrasound applicators appear most appropriate for more precisely controlled heating of somewhat deeper superficial tumors to at least 3 cm depth, and in some lower perfusion tumor nodules as deep as 6-8 cm. Computer controlled scanning of either MW or US sources has proven useful to further extend the surface area that can be heated with a given number of sources, and several scanning systems have demonstrated precise control of power deposition similar to or better than that of stationary array applicators.

The past two decades have seen a dramatic change in the resources available for thermal therapy of superficial tissues, from single aperture sources with only up/down power control to either multi-aperture stationary arrays or mechanically or electronically scanned arrays. Spatial control of power deposition is often limited now by the available feedback control information, which also is changing rapidly from the sparsely sampled discrete points around implanted needle thermometers of yesterday towards: i) more sophisticated invasive probes that monitor multiple temperatures and/or physiologic responses to therapy; ii) treatment plan based computer interpolation of complete temperature distributions; and iii) real-time non-invasive monitoring of 2-D and 3-D temperature and physiologic response distributions. Major impediments to increased use of clinical hyperthermia at the present are the limited number of applicators that have been truly optimized for heat treatment a specific anatomic site or condition, poor availability of the recently improved systems, and low reimbursement which slows commercial implementation of recent developments. Continued effort is required to bring some of the complimentary older systems up to date and especially to make the improved site optimized equipment available throughout the hyperthermia community.

TABLE 1. Devices and Techniques for Superficial Tissue Hyperthermia

Electromagnetic Techniques	**References**
Single Aperture Waveguide (430-2450 MHz)	57, 58, 151, 195-200
Adjustable Absorbing Bolus (Multi-section Saline Pad)	59, 60
Lens Applicator (433 MHz, Metal Vanes)	61-64
Robot Scanned Waveguide Applicator	66, 67
Dual Waveguide Applicator (200-915 MHz)	70,71
Dual Horn Applicator (87-400 MHz TEM)	36
Spherical Slot Array (2450 MHz, Concentric ring slots)	201
Spiral Microstrip Conformal Array (915 MHz)	69, 96
Scanning Spiral Microstrip (433 MHz, 1-2 Aperture)	68, 69
Multielement Waveguide Planar Array (915 MHz, 16 Apertures)	72, 73
LCA-Lucite Cone Applicator (434 MHz Modified Horn)	83-86
Microstrip-Slot (915, 434 & 2450 MHz, 1 & 3 MHz Radiometry)	87, 89
CSA-Current Sheet Applicator (915 or 433 MHz)	75-80
CFMA-Contact Flexible MW Applicator (434 MHz Microstrip)	98, 99
CMA-Conformal MW Array (915 or 433 MHz PCB Microstrip Array)	100-104, 106, 107
Ultrasound Techniques	
Single Transducer (1-5 MHz Piston Style)	109, 202-204
Concentric Ring Applicator (Multielement 1.0 MHz, 10 cm dia)	205
Multielement Transducer Planar Array (1,3.5 MHz, 16 Apertures)	52, 113-116
SURLAS - Scanning Reflector Ultrasound Array (1-5 MHz)	129-131
SFUS–Scanned Focused Ultrasound (1-4 MHz)	117, 120, 121
Cylindrical Array Breast System (1.8-4.8 MHz)	122
SSA - Spherical Section Array	126
CSA - Cylindrical Section Array	125
Sector Vortex Array	124
Field Conjugate Acoustic Lens	128
Large Volume Deep and Superficial Heating Sources	
Ridged waveguide (27.12 MHz, Tangential E)	206, 207
Thermotron RF-8 Radiofrequency Capacitive Plates (8-13 MHz)	132
Sigma-60 phased array (60-120 MHz, 8 dipoles, Axial E Field)	208
Sigma Eye elliptical array (100 MHz, 24 dipoles, with MRI)	138
MPA - Matched Phased Array (70 MHz Waveguides)	140
HEMA–Hybrid Evanescent Mode (10-30 MHz)	143

Table 2. SAR Coverage of Stationary Superficial Microwave Applicators (915 & 434 MHz)

Manufacturer (Frequency)	Type	Applicator Size (cm)	Coupling Bolus	1 cm Depth		Reference
				Area>50% SAR_{max}	Area>50% SAR_{max} Aperture Area	
(915 MHz)						
Clinitherm Corp.	Single Waveguide	7.5 x 7.5	1 cm DI Water	5 x 5	44	Straube [58]
"	"	10 x 10	"	8 x 8	64	"
"	"	10 x 10	2 cm Mineral Oil	6 x 7	42	"
"	"	15 x 15	"	8.5 x 7.5	28	"
BSD Corp.	"	13 x 10	1 cm DI Water	6x8.5	39	"
"	"	24 x 17.5	0.5 cm DI Water	11.5 x 10.5	29	Sherar [59]
"	"	"	Absorbing Bolus	15.5 x 13.5	50	"
"	"	"	Var. Absorbing Bolus	16.5# x 14.5	57 #	Sherar [60]
Lund Science	"	9.4 x 9.4	Direct Contact	9 x 4.2 *	43 *	Nilsson [70]
Labthermics Tech.	Single Waveguide	3.8 x 3.8	3 cm DI Water	6 x 4 +	166 +	Diederich [73]
	Waveguide Array of 4	7.5 x 7.5	"	8 x 9	128	"
"	Waveguide Array of 16	15 x 15	"	15 x 15	100	"
Stanford U.	Single Microstrip Spiral	3.5 Dia.	1.5 cm DI Water	2.2 x 1.8 **	41 **	Lee [96]
"	"	3.5 Dia.	3.8 cm DI Water	5.5 x 5 **	286 **	"
"	Microstrip Spiral Array 25	18.5 x 18.5	"	20 x 20 **	117 **	"
UC San Francisco	Dual Concentric Conductor	4 x 4	0.6 cm DI Water	5 x 5	156	Rossetto [103]
"	DCC Array of 4	9.5 x 9.5	0.6 cm DI Water	10 x 10.5	116	Stauffer [107]
"	DCC Array of 16	20.5 x 20.5	0.6 cm DI Water	21 x 21.5	107	This Work
(434 MHz)						
U. Arizona	Current Sheet - CSA	7.3 x 5.9	Direct Contact	5.5 x 4	51	Gopal [77]
"	CSA Array of 4	14.5 x 11.5	"	12 x 10	72	"
U. Amsterdam/Istok	Contact Flex Microstrip -1H	7.2 x 19.7	1.5 cm DI Water	4.7 x 13.5 ^	45	Lamaitre [98]
"	CFMA – 3H	28.7 x 20.7	1.7 cm DI Water	17.7 x 17.5 ^	52	"
"	CFMA – 5H	19.7 x 29.5	1.0 cm DI Water	12.5 x 24 ^	52	"
U. Rotterdam	"Conventional" Horn	10 x 10	1.0 cm DI Water	4.6 x 7.8	36	Van Rhoon [83]
	Lucite Cone Applicator-LCA	10 x 10	"	7.6 x 13.5	103	"

Areas > 50% SAR calculated as the average of elliptical and rectangular areas defined by two orthogonal dimensions in plane 1 cm deep in phantom.

\+ Average of three apertures in different positions within the planar array

* Measured 2 mm deep in phantom rather than 1 cm deep

** Measured 4 mm deep in phantom rather than 1 cm deep

\# Data shows 14.5 cm or 1 cm increase in lateral extent of 50% SAR in one direction only, 16.5 cm obtained by adding 1 cm in other dimension to Sherar [59]

^ Measured 1 cm deep in saline phantom

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