CHAPTER

21 Hyperthermia

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The biological rationale for hyperthermia (HT) as a cancer treatment is based on several mechanisms, particularly relating to its combination with other therapies: (1) HT is directly cytotoxic. (2) When used with radiotherapy (RT), HT inhibits potentially lethal- and sublethal-damage repair and has complementary cytotoxicity with reference to the cell cycle. Hyperthermic killing is not influenced by hypoxia, whereas hypoxia has a significant effect on radiosensitivity. HT causes reoxygenation, which can increase RT sensitivity. (3) HT increases drug uptake into cells, enhances DNA damage, and partially or completely reverses drug resistance. (4) HT improves delivery of nanoparticle drug carriers, such as liposomes, and macromolecular drugs, such as antibodies and drug-carrying polymers. (5) The process of thermal adaptation (thermotolerance) may enhance exposure of tumor cell antigens to immune cells and increase innate immunity, thereby augmenting host immune responses against tumor cells.

Despite strong biological rationale, delivery of HT presents significant challenges. The goal is to be able to heat tumor tissue volumes reproducibly and to do so using methods that are clinically practical. A significant impediment to this goal is that current thermometry is invasive. Consequently, definition and calculation of thermal dose is not well defined. Priorities in the area of engineering and physics center on improvements in technologies to deliver HT, to measure thermal dose noninvasively, and to use such data to control power to the tumor in real time.

Despite the technical difficulties in delivering HT, however, several positive randomized trials using HT in combination with RT and chemotherapy in human patients with cancer have been published in addition to three positive canine randomized trials. The majority have demonstrated local control or survival advantages with therapies involving HT. These trials have involved patients with cervix cancer, primary brain tumors, head and neck cancers, esophageal cancer, chest wall recurrences of breast cancer, bladder cancer, melanoma, and most recently, high-grade soft-tissue sarcomas.

In this chapter, the biological rationale for using HT will be examined in more detail, a survey of methods used to heat tissues will be provided, and a comprehensive overview of key Phase III studies will be presented. The emerging discipline of thermal ablative technologies will also be presented briefly because it is approved for treatment of a range of diseases and is used widely by interventional radiologists and surgeons.

THE BIOLOGY OF HYPERTHERMIA

Definition of Hyperthermia

Hyperthermia means elevation of temperature to a supraphysiologic level, between 40°C and 45°C. Typical durations of hyperthermia treatment are 30 minutes to 60 minutes a session. Temperatures in the range of 50°C to 100°C for a few minutes per session are used for thermal ablation.[1]

The Arrhenius Relationship and Thermal Isoeffect Dose

Arrhenius found a temperature dependence of sucrose hydrolysis in the presence of various acids that was a logarithmic function of the absolute temperatures at which the reactions were conducted.[2] These observations were physiologically relevant in that the rate of cellular metabolism increases as temperature rises in cells or tissues, up to a point where thermal damage is created. The principles discovered by Arrhenius extend to cell killing by HT as well. The temperature dependence of the rate of cell killing is referred to as the "Arrhenius relationship."

The temperature dependence of the rate of cell killing has been used as a method for thermal dosimetry. This is done by plotting temperature versus log of the slope of the survival curve ($1/Do$). Do is analogous to a Do in a radiation survival curve (the dose to reduce survival to 37% of a starting value on the exponential portion of the survival curve). In the case of HT, "dose" is the number of minutes at a specified temperature (Figure 21-1). Typically, Arrhenius plots have a biphasic curve and the point at which there is a change in slope is referred to as a *breakpoint*. Above the breakpoint for nearly all cell types, a change in temperature of 1.0°C doubles the rate of cell killing. Acquired resistance to HT killing (thermotolerance) that occurs during HT is responsible for the change in slope of the heat cell survival curve at longer heating times for temperatures below 43°C (see Figure 21-1, *A*). Arrhenius plots for human cell and rodent lines are well described. The breakpoint for human cells is near 43.5°C, and the slope below the breakpoint, which is caused by thermotolerance induction during heating, is between 2 and 4. The slopes of Arrhenius plots derived from in vivo studies are virtually identical to those that are derived from in vitro studies.[4]

Sapareto and Dewey[5] proposed using the Arrhenius relationship to normalize thermal data from HT treatments. The rationale came from the observations that time-temperature histories are not stable, that they vary from patient to patient, and that temperatures within tumors were almost always nonuniform. Using the Arrhenius relationship, it would be possible to convert all time-temperature data to an equivalent number of minutes at a standard temperature (defined as 43°C). The formulation takes the following form.

$$\text{CEM } 43^\circ\text{C} = t R^{(43-T)} \qquad \text{Equation 1}$$

Where CEM 43°C = cumulative equivalent minutes at 43°C (the temperature most commonly used for normalization), t is the time of treatment, T is the average temperature during desired interval of heating, and R is a constant. When above the breakpoint, which is assumed by convention to be 43°C, $R = 0.5$. When below the breakpoint, $R = 0.25$

For a complex time-temperature history, the heating profile is broken into intervals of time t length, where the temperature remains relatively constant. CEM 43°C is calculated using the average T (T_{avg}) for each interval, and the resultant data

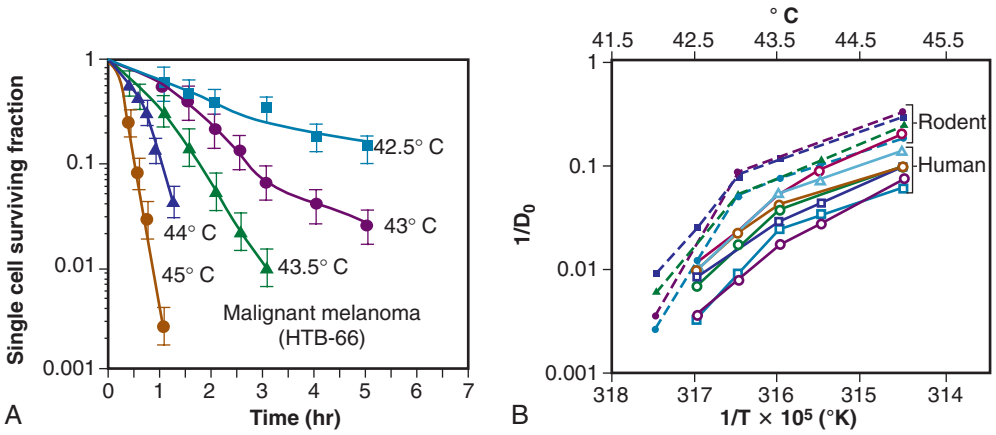

Figure 21-1 **(a)** Cell survival curves for human melanoma cells, plotted as log of surviving fraction as a function of time of heating at a defined temperature. **(b)** Arrhenius plots derived from survival curve data of several human and rodent tumor lines. Note change in slope (known as the "breakpoint") of Arrhenius plots for both types of cells. For human cell lines, this appears to be around 43.5° C, whereas for rodent lines it is approximately 43° C.
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are summed to give a final CEM 43°C for the entire heating regimen.

$$\text{CEM } 43^\circ\text{C} = \Sigma t R^{(43-T_{avg})} \qquad \text{Equation 2}$$

The CEM 43°C (thermal isoeffect dose) formulation has been used extensively and successfully in clinical trials to assess the efficacy of heating. This is despite that the *R* values and breakpoints have historically been derived from studies done in rodents, which are somewhat different from the parameters derived from human cells.[4]

There appears to be a relatively common threshold for thermal coagulation, which is used for thermal ablation. CEM 43°C >240 minutes is sufficient to achieve full coagulation of most tissues.[1]

Mechanisms of Hyperthermic Cytotoxicity

Cellular and Tissue Responses to Hyperthermia

Protein Is the Primary Target for Hyperthermic Cytotoxicity

When cells are exposed to elevated temperatures (≥41.0°C), damage is inflicted in multiple sites, but the predominant molecular target appears to be protein. The heat of inactivation for cell killing and thermal damage to tissues is in the range of that necessary for protein denaturation (130 kcal/mole to 170 kcal/mole).[6] Additional evidence for proteins as being the primary target for cell killing is the importance of heat shock proteins in protecting thermotolerant cells from thermal damage. One of the primary functions of heat shock proteins is to refold other proteins that have been damaged.[7]

Some organelles are especially important in controlling thermal response. For example, modification of membrane lipid content or use of membrane active agents, such as alcohols, can sensitize cells to heat killing, but the sensitization is probably related to destabilization of the membrane as it relates to lipid-protein interactions.[8] The cytoskeleton of cells is particularly heat sensitive.[9] When it is collapsed by heat, there is disruption of cytoskeletal-dependent signal transduction pathways as well as inhibition of cell motility.[10,11] The heat sensitivity of the centriole leads to chromosomal aberrations following thermal injury.[12] Finally, the DNA repair process is heat sensitive, and this may be one of the mechanisms that leads to heat-induced radio- and chemosensitization.[13]

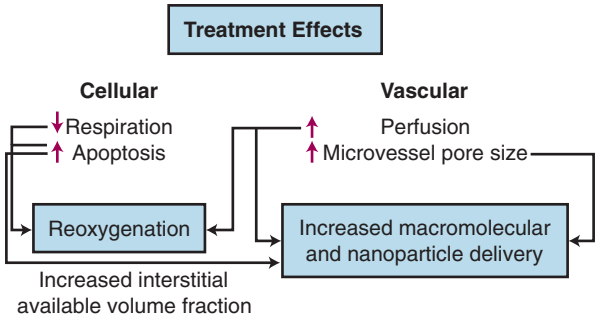

Figure 21-2 Overview of the beneficial physiologic and metabolic effects of HT.

Physiologic Response to Hyperthermia

Tumor blood flow and metabolism have important influences on the efficacy of HT, and conversely, the physiologic consequences of HT can influence the efficacy of other treatments.

As temperatures are increased, there is an increase in blood flow. The temperature threshold for this change is 41°C to 41.5°C in skin.[14] Changes in vascular permeability also occur, leading to edema formation in the heated volume. At higher thermal doses, vascular stasis and hemorrhage develop. The change in normal tissue perfusion upon heating is much greater (10-fold) than one sees in tumors (1.5- to 2-fold).[15] Mechanisms underlying vascular stasis may include arteriovenous shunting, thrombus formation, and leukocyte plugging.[16] Importantly, physiologic changes occur in tumors at temperatures below those that damage normal tissue (Figure 21-2).

Taking Advantage of Physiological Response to Hyperthermia

Improvement in Macromolecular and Liposomal Drug Delivery. A liposome is a small lipid vesicle (≈100 nm diameter) that contains water or saline in the center. Drugs can be loaded into liposomes at high concentration. HT increases microvascular pore sizes preferentially in tumor microvessels, which leads to enhanced liposomal accumulation in tumor.[17] The threshold for increased liposomal extravasation is 40°C

and increases by a factor of two for every degree temperature rise until vascular damage occurs.[18] The effects of HT on liposomal extravasation have been studied extensively in preclinical models, but 2-fold to 13-fold enhancement in accumulation occurs in spontaneous soft-tissue sarcomas of pet cats, an encouraging result that may translate to human tumors.[19] HT also increases the available volume fraction (fraction of tissue not occupied by cells or stromal fibers), which may develop as cells undergo either necrosis or apoptosis following heat treatment.[20] This increases the tissue space available for nanoparticles to be deposited. The increase in liposomal drug delivery achieved with HT has been shown to result in increased antitumor effect in many preclinical studies.[21] HT has been used in conjunction with liposomal doxorubicin and radiation in one small clinical series of patients with chest wall recurrences of breast cancer and encouraging results were obtained.[22]

Selective delivery of drug to a targeted tumor volume can be enhanced by using thermosensitive liposomes. These liposomes undergo a phase transition from a solid to a liquid state as they are heated.[23] When the phase transition occurs, the liposomes become permeable and release their contents. The phase transition temperature can be modified by changing the lipid composition. The original idea for a thermosensitive liposome is attributed to Dr. Milton Yatvin,[24] but the phase transition temperature of his formulation was too high and the rate of drug release was too slow for clinical use.[24] Needham developed the first low temperature, rapid release thermosensitive liposome, which exhibited complete doxorubicin release in <20 seconds upon reaching a transition temperature of 41.3°C.[25] Since then, other formulations have been reported that exhibit similar properties.[26,27] A key feature of this liposome is the fact that the majority of drug delivery achieved is via intravascular drug release (Figure 21-3). This feature essentially creates a local drug infusion within the heated volume that drives the drug down its concentration gradient and into the tumor interstitial space. This feature yields significantly greater drug penetration than can be achieved by increasing pore sizes to solid liposomes.[28] The Needham doxorubicin-loaded formulation yielded 5-fold higher accumulation of drug following HT treatment of 60 minutes at 42°C than the nonthermally sensitive Doxil formulation and 25-fold higher accumulation than free drug. The antitumor efficacy of the Needham formulation with HT was substantially greater than the liposomal drug without HT or free drug with HT in several different tumor lines.[29] The degree of enhancement in antitumor properties was directly proportional to the amount of drug accumulation in tumor.[30]

For relatively small chemotherapeutic drugs, there is no advantage gained via increased vascular permeability to macromolecules or nanoparticles, unless the drugs are protein-bound.[31] For drugs with molecular weight <1000 mw, the primary mechanism that governs drug transport is diffusion,[32] which is not highly temperature dependent. In contrast, the primary driving force for transport of macromolecules with >1000 mw is convection, which is controlled by the pressure gradient across the vessel wall. Accordingly, HT can augment the transvascular delivery of agents such as monoclonal antibodies[33] and polymeric peptides that carry drugs or radioisotopes.[34] Dreher et al used a novel peptide polymer that undergoes an inverse phase transition at 41°C, to "pump" polymer into tumors. The inverse phase transition refers to a

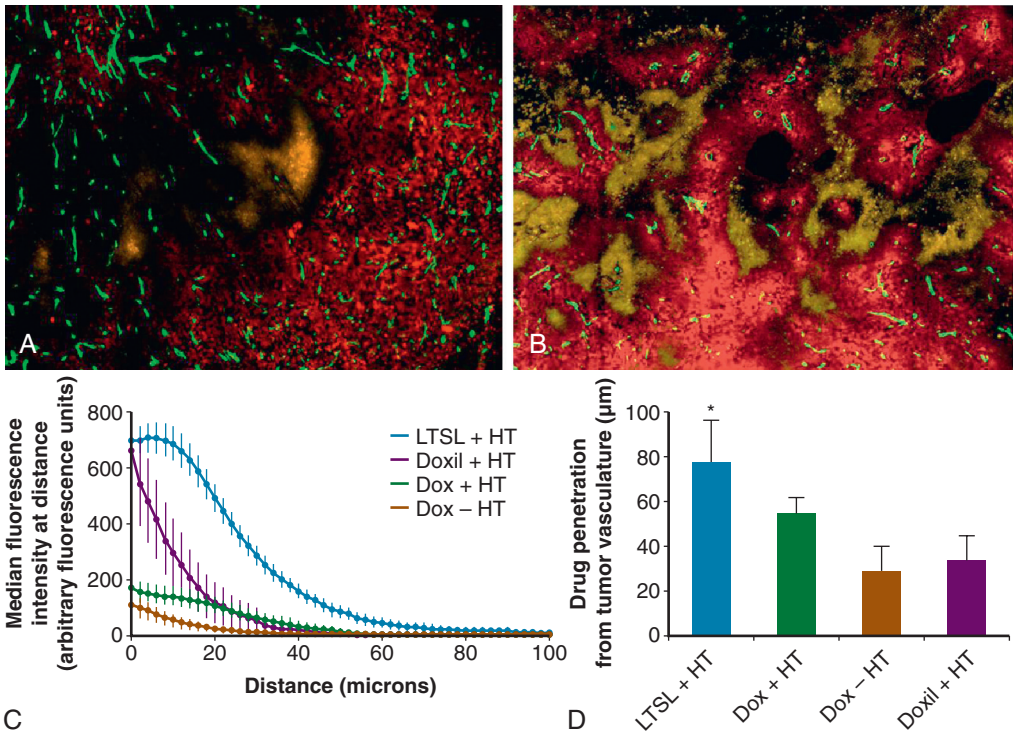

Figure 21-3 Immunohistochemistry images of doxorubicin penetration (red fluorescence) from vessels in the FaDu head and neck tumor xenograft. **A** and **B,** histology images following free doxorubicin with 42°C heating **(A)** and thermosensitive doxorubicin containing liposome (Dox-LTSL) with heating **(B).** Microvessels were stained with CD31 (green), and tissues assessed for hypoxia, using EF5 *(yellow)*. Qualitatively, the drug penetration is far greater with Dox-LTSL than with free drug. Quantification of penetration distance from nearest blood vessel shows that Dox-LTSL + heat delivers more drug at all distances from vessels compared with Doxil™ and free doxorubicin with heat **(C).** Doxorubicin delivered with Dox-LTSL penetrates twice as far as Doxil™ liposomes (78 vs. 34 mm; $p = 0.0106$) **(D).**
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physical feature of the polymer that renders it to be water soluble below 41°C; above this temperature, the polymer comes out of solution in aggregates. The aggregation occurs primarily intravascularly but is reversible. Thus, when the tissue is cooled down, the particles rapidly disaggregate and diffuse into the tissue down their concentration gradient.[35] Additional nanoparticles have been designed since this work, which also have attractive thermal properties that would enhance drug delivery.[36,37]

Effects of HT on Tumor Metabolism and Oxygenation. Heat also modulates cell metabolism, by switching it toward glycolysis. This reduces oxygen consumption rate, which, in combination with increased perfusion, may contribute to heat induced reoxygenation.[38] Decreases in ATP concentration after HT are inversely related to the temperatures achieved during HT in preclinical models and canine sarcomas[39,40] and are related to pathologic CR rate in human sarcomas.[39] Decreases in ATP and increases in lactate concentration occur following tumor blood flow reduction after HT.[41] In human patients with soft tissue sarcomas who were treated preoperatively with HT and radiation therapy, reduction in ATP/Pi ratio (measured using ^{31}P magnetic resonance spectroscopy; Pi = inorganic phosphate) was significantly correlated with a higher probability for pathologic complete response.[39] These results are consistent with the theory that tumor respiration decreases after HT treatment.

Several pre-clinical studies have shown that mild temperature heating (between 40°C and 42°C for an hour) can lead to improvements in tumor pO_2 up to 24 hours after heating.[42] However, in some models, the extent of reoxygenation is quite heterogeneous between and even within individual tumors.[43] It has been reported that HT improves tumor oxygenation in canine and human soft tissue sarcomas, with reoxygenation being associated with greater probability for pathologic complete response (pCR) in human tumors.[44,45] In a canine study, median temperatures <44°C improved oxygenation, whereas median temperatures >44°C for 60 minutes led to decreased oxygenation.[44] In a follow up study with canine sarcomas, reoxygenation 24 hours after the first heat treatment was associated with increased likelihood for reduction in tumor volume at the end of therapy.[46] In patients with locally advanced breast cancer who were treated in a phase II study with preoperative HT + radiotherapy and taxol, there was a significantly increased likelihood for achieving pCR if the tumors reoxygenated 24 hours after the first HT treatment. The probability for achieving a pCR was greater when the median temperatures were below 41.5°C.[47] Improvement in oxygenation does not occur in all tumors, however, and currently there is no method for predicting which tumors will show this effect.[48] In summary, mild temperature elevations during HT will benefit some patients if HT induces reoxygenation. To take full advantage of this effect it will be necessary to utilize methods to enhance the reoxygenation effect, such that it occurs in the majority of patients. Song and Griffin have suggested that the addition of hyperoxic gas breathing after HT, but during radiotherapy, may achieve this goal.[49,50]

Hyperthermia and Metastases

HT causes abrupt changes in tumor microvascular function, as described above, which could enhance tumor cell shedding from the heated site. Pre-clinical studies are mixed on this issue. One report showed that local HT alone enhanced the metastatic rate of B16 melanoma.[51,52] When curative doses of radiotherapy were added to HT in the B16 melanoma model, however, the incidence of lymph node and lung metastases was decreased, compared with controls.[52] The combination of curative doses of radiation and HT has generally been reported in other tumor models to reduce the incidence of metastases,[53,54] although in a few models, simultaneous administration of HT with radiation has been reported to increase metastases.[53,54]

The question of whether local HT increases the risk for metastasis is difficult to answer in clinical trials unless the primary therapy has a high probability for local control. This is because of the problem of competing risks. In a phase III trial of canine patients with primary malignant melanomas treated with the combination of HT and radiation or radiation alone, no difference in the likelihood for metastasis between the two groups was seen.[55] However, local recurrence was a common event, and its onset was frequently followed by appearance of distant metastases. In a phase III randomized trial of human melanomas treated with thermoradiotherapy vs. radiotherapy alone, there was significant improvement in the likelihood for survival when the local tumor was controlled. Since the use of HT in that trial resulted in improved local control, the implication is that the combination therapy reduced the probability for metastases.[56,57] In a study comparing graded doses of radiation ± HT for treatment of canine soft-tissue sarcomas, higher normal tissue temperatures in the region of the tumor were correlated with lower likelihood for distant metastases.[58] A large series of patients (N = 95) with previously untreated high-grade soft tissue sarcomas who were treated preoperatively with HT and radiation achieved a local control rate near 90%, but 50% developed distant metastases.[59] This rate of metastasis is essentially identical to that seen with preoperative RT alone, however, suggesting that HT had an undetectable influence on metastases.[60]

The conclusion is that with the exception of one study with the B16 melanoma murine model involving HT alone, there is not any evidence from pre-clinical models or human trials that local-regional HT causes an increase in metastases, particularly when HT is combined with radiotherapy.

Normal Tissue Damage from Hyperthermia

Thresholds for thermal damage depend on the tissue type being heated and the severity of the injury. Mild damage can merely lead to edema, whereas more severe injury can lead to massive necrosis and organ failure. This subject has been reviewed in detail.[1,3] The ranking of tissue thermal sensitivities does not follow classical principles derived from other cytotoxic agents, such as radiation or chemotherapy. With such agents the most sensitive tissues are those with the highest proliferative potential or activity. For HT the most sensitive tissue classification includes brain, which is comprised of cells with almost no proliferative potential, as well as testis, which has high proliferative potential. There has been speculation as to whether tumor tissues might be more sensitive to thermal damage than normal tissues. Many studies have compared tumor to normal cells, in vitro. There is no inherent difference in the thermal sensitivity. However, the microenvironment of tumors, which is often acidotic and nutritionally deprived, leads to an increase in thermal sensitivity that has been reported in a clinical series.[61]

Radiation and Hyperthermia

Rationale for Combining Hyperthermia with Radiotherapy

When radiation is combined with HT, complementary effects occur. Cells in S-phase are radioresistant, but sensitive to HT. Hypoxic cells are three-fold more resistant to radiation, compared to aerobic cells, but there is no difference in thermal sensitivity between aerobic and hypoxic cells. As discussed

earlier, HT can lead to reoxygenation, which will further improve radiotherapy response.[42,45,46,62] Finally, HT inhibits the repair of both sublethal and potentially lethal damage by inactivating crucial DNA repair pathways.[63-65]

Factors to Consider When Combining Hyperthermia with Radiotherapy

The interaction between radiation and HT is described by the "thermal enhancement ratio" or TER, which is defined as the ratio of doses of radiation to achieve an isoeffect for RT/RT + HT. TERs for local tumor control have been estimated for a number of human tumors using historical control data for radiation alone.[66] In most tumor types examined, these ratios were >1. Assessment of normal tissue TER has not been attempted except in a few cases. For those examples, TER values for normal tissue damage have been less than those for tumor in the same patient population, suggesting potential for therapeutic gain for RT + HT compared with RT alone.[66] Prospective randomized trials in dogs with spontaneous tumors have also shown evidence for improved local tumor control with RT + HT compared with RT alone[58,67-69] with no observable increase in the frequency of clinically relevant late normal tissue complications. In one canine trial enhancement of late radiation damage (as assessed histologically) was reported and the duration of acute radiation complications was prolonged.[69] There is clinical evidence, however, that excessively high intratumoral temperatures (i.e., >45°C for 60 minutes) can lead to damage to surrounding normal tissues, an effect that is often caused by rapid tumor regression.[67,70] Such damage is not easily repaired and can lead to chronic tissue consequences, such as fibrosis, fistulae formation, and bone necrosis.

Two cases of fatal pelvic necrosis have been reported as a late complication in patients with locally advanced cervix cancer treated with thermoradiotherapy.[71] There was speculation as to whether the complication was the result of HT. More recently, however, this rare complication has been reported following chemoradiotherapy treatment of cervix cancer.[72,73] Thermal doses achieved in the HT series were several degrees lower than has been reported to be associated with enhancement of normal tissue complications by radiotherapy, which strongly suggests that these two cases were not the result of HT, but more likely a result of the radiotherapy treatment, perhaps complicated by a heavy smoking history associated with both patients.[71]

In summary, most available data from pre-clinical and clinical studies indicate that therapeutic gain is achievable for the combination of HT with RT. There is very little evidence to suggest that HT enhances the incidence or severity of late normal tissue complications from radiotherapy, particularly when excessively high intratumoral temperatures are avoided.

Hyperthermia and Chemotherapy

Rationale for Using Hyperthermia with Chemotherapy

Many chemotherapeutic agents have been shown to exhibit synergism with HT, including cisplatin and related compounds, melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosoureas, blyeomycin, mitomycin C, and hypoxic cell sensitizers.[31] The mechanisms that underlie the synergy may include: (1) increased cellular uptake of drug, (2) increased oxygen radical production, (3) increased DNA damage and inhibition of repair, and (4) reversal of drug resistance mechanisms.[74-77] Hypoxia and pH are also important in the thermochemotherapeutic response.[78-82] There are some classes of drugs, such as etoposide and vinca alkaloids, that do not synergistically interact with HT.[31]

Rationale for Using Hyperthermia with Targeted Agents

(MAP) Kinase, Heat Shock Response and HIF-1

It has been reported that hyperthermia can increase expression of HSP40 (40 KD heat shock protein) via the ERK1/2 (MAP) kinase pathway.[83] The upregulation of HSP40 protects against heat killing, but blockade of MAP kinase activation by SiRNA or by targeted drugs sensitizes tumor cells to hyperthermic cell killing.

HIF-1 is also upregulated by hyperthermia in a process mediated by ERK1/2 transcription of NADPH oxidase in tumor cells.[38] The increased production of peroxide by NADPH oxidase stabilizes the labile subunit, HIF-1α. Increased levels of HIF-1α bind to its heterodimer, HIF-1β, leading to HIF-1 mediated gene transcription. The increased transcriptional activity of HIF-1 upregulates: (1) production of VEGF (vascular endothelial growth factor), which promotes angiogenesis and (2) PDK-1, (pyruvate dehydrogenase lipoamide kinase isozyme 1) which promotes a switch to anaerobic metabolism. Both of these responses and other HIF-1 regulated genes promote survival of tumor cells. The upregulation of HIF-1 mediated transcripts has been verified clinically in canine sarcomas after treatment with thermoradiotherapy.[84] Further, inhibition of HIF-1 after radiotherapy has been shown to enhance growth delay.[85] Thus, there is rationale to inhibit the HIF-1 response after hyperthermia particularly when combined with radiotherapy.

Genomic Analyses

Genomic analysis of U937 cells, a human myelomonocytic tumor, exhibited differential expression in approximately 1000 genes, following a non-cytotoxic treatment of 41°C for 30 minutes.[86] A higher thermal exposure of 42°C for 90 minutes led to more significant change in pro-apoptotic signaling pathways,[87] in addition to the expected heat shock response in both cases. Genome-wide analysis has also been done on one rat tumor line in vivo, following local heating (43°C for 60 minutes).[88,89] The effects of hyperthermia were rather pleiotropic, involving over 1200 genes and a host of cellular responses, including apoptosis regulation, cell cycle control, MAP kinase and calcium regulated cell signaling and genes involved in angiogenesis and metabolism regulation. There was also substantial downregulation of a number of genes involved in immune function at 3 hours after treatment, which recovered to baseline by 24 hours. These results suggested that HT does not adversely affect immune function. The fact that hyperthermia appears to augment pro-apoptotic signaling pathways suggests that it could work additively to with targeted agents that promote apoptosis.

Chi et al conducted the first clinical study comparing gene expression patterns and functional imaging (diffusion weighted MRI) prior to and 24 hours after the first HT fraction during a course of thermoradiotherapy for spontaneous canine soft tissue sarcomas.[84] Patterns of gene expression change of VEGF, DNA repair and inflammation were correlated with response, as assessed by changes in diffusion weighted MRI. Using connectivity mapping, the differential in gene expression was found to be linked to several drugs, the most promising of which was geldanomycin, an HSP90 inhibitor. The authors went on to show that this drug sensitizes cells to thermoradiotherapy, in vitro. This provides rationale for such combinations in future human clinical trials.

PARP-1 (Poly [ADP-ribose] Polymerase 1) Inhibitors

It has recently been reported that mild hyperthermia (41°C and 43°C) inhibits double strand DNA break repair after

radiotherapy.[90] This is due to downregulation of BRCA2 accumulation at double strand break sites of DNA. BRCA2 is a protein that is essential for completion of homologous recombination. Based on prior knowledge that cells deficient in BRCA2 are sensitive to PARP-1(Poly [ADP-ribose] polymerase 1) inhibitors, the authors went on to show that inhibition of PARP-1 sensitizes tumor cells to killing by hyperthermia. The authors termed this strategic approach an "induced synthetic lethality." Given that PARP inhibitors are currently in clinical trials <http://clinicaltrials.gov/ct2/results?term=PARP+inhibitor&Search=Search>, this therapeutic approach may be rapidly translated to trials involving hyperthermia.

It has been reported that HT can induce autophagy via activation of NFκB, as a protective mechanism against cell death.[91,92] Thus it would make sense to consider combining agents that inhibit NFκB activation with HT as a means to enhance thermal cell killing. Alternatively, the combination of 43°C hyperthermia with increased oxidative stress can increase cell killing via inhibition of the Akt pathway and induction of irreversible autophagy.[92] Pajonk et al reported that inhibition of proteasome activity in combination with (44°C for 60 minutes) hyperthermia was particularly effective in augmenting apoptosis, in addition to causing substantial radiosensitization.[93]

In summary, there appears that there is emerging rationale for targeting various signal transduction pathways and other cellular adaptation processes as a means to enhance cell killing when combined with hyperthermia.

Factors to Consider when Combining Hyperthermia with Chemotherapy

Temperature Dependence

The degree of enhancement of cytotoxicity has been shown to be temperature dependent for many drugs.[94] Combinations of camptothecins with HT have not shown consistent results in vitro. The interaction between these agents and HT is schedule and temperature dependent.[95,96] In one report, temperatures up to 41.8°C increased the activity of topoisomerase II, which may be the explanation for the increased activity of these drugs at elevated temperatures.[95]

In Vitro Results May not Predict In Vivo Activity

Tubulin binding agents, such as taxol, show no evidence for interaction in vitro,[97] but studies in combination with radiation therapy in vivo are more encouraging.[98] There may be physiologic consequences of the combination of taxol and HT that make the combination work better than predicted from in vitro studies.

Sequencing

For most drugs (excluding 5-FU and perhaps other antimetabolites), the optimal sequence between heat and drug is to administer them simultaneously or to give the drug immediately before the onset of heating. For platinum-containing drugs, the tissue extraction rate is increased with HT, further substantiating the rationale for use of this sequence.[99] It has been shown recently that thermal enhancement of cisplatin uptake by cells is the result of multimerization of the CTR1 transporter (otherwise known as the copper transporter).[100] Most antimetabolites do not interact with HT when given concomitantly.[31] However, 5FU has been shown to interact supra-additively with HT by controlling temperatures to be between 39°C and 41°C. Temperatures in this range lead to enhanced conversion to active metabolites, thereby increasing drug cytotoxicity. In addition, continuous infusion protocols with this drug may lead to cell cycle block in S phase, a relatively sensitive part of the cell cycle to HT.[101]

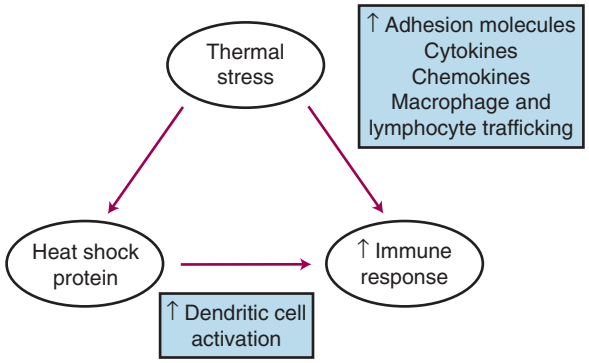

Figure 21-4 Summary of known beneficial immunological effects of mild temperature hyperthermia.

Immunological Effects of HT

Heat shock proteins have been recently recognized for their potential role in regulating immune responses. There are several recognized functions of these proteins: (1) They are known to bind, in a non-covalent fashion, to immunogenic peptides. (2) When tumor cells are exposed to HT, HSP-peptide complexes are presented on the cell surface. These complexes can be recognized by antigen-presenting cells (dendritic cells) via MHC class I molecules. Once dendritic cells have received this type of stimulus, they migrate to lymph nodes, where they prime T-cell lymphocytes to be cytotoxic toward cells that express the peptide-HSP complex. Hyperthermia has been shown to enhance the rate of dendritic cell migration.[102] (3) Heat shock proteins also induce dendritic cell maturation and pro-inflammatory cytokine release.[103,104] (4) Cell membrane localization of heat shock proteins also activates the innate immune system by activating natural killer cells (NK cells).[105] Other sources of cellular stress—such as viral infection, fever, hypoxia, and radiation exposure—have been shown to upregulate heat shock proteins as well. Because this process appears to occur naturally, there have been efforts to exploit the use of hyperthermia to produce tumor-derived vaccines and to augment the in vivo response to such vaccines.[104] HT has also been reported to upregulate a number of pro-inflammatory cytokines and adhesion molecules that facilitate immune cell trafficking across endothelial cells to gain access to tumor interstitium.[106] Additionally, shed heat shock proteins, with or without associated peptides, may act as chemokines to attract immune cells (particularly macrophages) toward a region tissue that has undergone heat stress.[107] A summary of some key immunological effects of HT is shown in Figure 21-4. Note that a special issue of the International Journal of Hyperthermia was recently published, which covers this subject in detail.[108]

HYPERTHERMIA PHYSICS/ENGINEERING

Clinical HT is usually achieved by exposing tissues to non-ionizing radiation (e.g., electromagnetic [EM] or ultrasonic [US] fields) or by conducting heat into tissue from a heated source (e.g., hot pad or needle). Although these modalities deposit energy in tissue by different physical mechanisms, they have general similarities. Uniformity of heating is sensitive to the heterogeneity of tissue properties, geometry of blood flow, and practical problems of coupling the energy source into tissue. Hyperthermia can be delivered non-invasively with externally applied power sources or invasively by placing heat sources either interstitially or inside natural body cavities. An overview of non-invasive methods is provided below and is summarized in Table 21-1. Invasive

TABLE 21-1 Summary of Methods Used to Heat Tissues

Class	Method	Power Directed to Tumor Site?	Frequency	Coupling Medium	Invasive Thermometry Requirements	Advantages	Disadvantages
ELECTROMAGNETIC							
Superficial							
	Capacitive radiofrequency	Partially, by changing position and relative size of electrodes	5-30 MHz	Saline	RF-shielded EMI-resistant probes and readout electronics	Simple to operate	Superficial fat heats; use limited to thinner patients
	Microwave waveguide	Yes, by placing waveguide over tumor	433, 915, 2450 MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Simple to operate	Limited depth of heating; heat pattern dependent on tissue properties and applicator coupling
	Microwave array	Yes, by adjusting relative power to multiple antennas	433, 915, MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Adjustable size, shape and location of heating; available in planar or conformal arrays	Limited depth of heating
Deep							
	Magnetic induction	No	0.05-15 MHz	Air	RF-shielded EMI-resistant probes and readout electronics	Simple to operate; focus with implanted particles or seeds	Eddy currents follow path of least resistance; heating pattern controllable with particles or seeds
	Capacitive radiofrequency	Partially, by changing position and temperature of electrodes	5-30 MHz	Saline	RF-shielded EMI-resistant probes and readout electronics	Simple to operate	Superficial fat heats; use limited to thinner patients
	Phased radio-frequency arrays	Partially, by adjusting phase and amplitude of power from different antennas	70-150 MHz	Water	Non-perturbing EMI-resistant fiberoptic probes or high-resistance lead thermistors	Ability to focus heat at depth and move the heat focus around	Limited control over size and location of heat focus
ULTRASOUND							
Superficial							
	Planar non-focused ultrasound transducer	Partially, by placing transducers over tumor	1-5 MHz	Degassed water	Metal probes required; avoid plastic	Simple to operate	Good coupling to soft tissue required—air and air prohibit penetration and can lead to pain
	Planar non-focused ultrasound transducers—multiple	Yes, by adjusting relative power and/or frequency of transducers	1-5 MHz	Degassed water	Metal probes required; avoid plastic	Improved control of size, shape and perhaps depth of heating	Good coupling to soft tissue required—air and air prohibit penetration and can lead to pain
Deep							
	Focused transducer array	Yes, by adjusting relative power, phase and/or scanning of transducers	0.5-2 MHz	Degassed water	Metal probes required; avoid plastic	Precise steerable focus possible at depth	Practical limit on size and location of appropriate acoustic window, air and bone prohibit penetration and can lead to pain

methods have been developed extensively and include radiofrequency (RF) electrodes, microwave antennas, ultrasound transducers, hot water tubes, and inductively heated ferromagnetic implant rods or seeds. Further details on all methods are available elsewhere.[109-118]

Electromagnetic Heating

The primary mechanism of EM heating varies with frequency. For radiofrequency (RF) fields below about 30 MHz, the EM field induces a net movement of free electrons and power deposition results from resistive (ohmic) losses due to electric currents through lossy tissue. The term "lossy" means that the tissue is both a poor conductor and poor insulator. As such, electromagenetic fields are absorbed as they traverse the tissue. At microwave frequencies above about 150 MHz, heating results primarily from friction between polar water molecules that oscillate to maintain alignment with the time-varying field. This is called "dielectric loss." Improved penetration is obtained for lower frequencies with longer wavelengths, but the ability to localize EM energy in a desired target improves with higher frequency and corresponding shorter EM wavelengths. Accordingly, there is a trade-off between depth of penetration and ability to focus energy. In practice, heating may be localized in tumor targets within 2-4 cm from a microwave applicator at >430 MHz, whereas lower frequency multiple antenna phased arrays are used to heat larger regions that include tumor deep in the body.

Considering the effects described earlier, electromagnetic heating devices are quite different for superficial heat applications with effective penetration less than 4 cm than they are for deep heating of tissue more than 4 cm. Superficial heat applicators include waveguides (Figure 21-5) and microstrip or patch antennas (Figure 21-6) operating at microwave frequencies of 433, 915, or 2450 MHz. These devices can be separated into two categories: superficial applicators with effective penetration into tissue <4 cm, and deep heating devices that have effective penetration >4 cm. Superficial devices include waveguides (Figure 21-5) and microstrip or patch antennas (Figure 21-6) operating at microwave frequencies of 433, 915, or 2450 MHz.[115-117,119-121] Microwave energy is usually coupled into tissue through a temperature-controlled deionized water bolus to maintain skin temperature below 44°C.

In order to heat at depths >4 cm, radiofrequencies between 5 and 200 MHz are used. There are three basic techniques for EM deep heating: inductively coupled magnetic fields, capacitively coupled electric fields, and radiated fields from multiple antenna phased arrays.

Magnetic Induction Heating

Magnetic induction heating uses a 0.05-15 MHz magnetic field to induce eddy currents in conductive tissue.[122] The magnetic field can penetrate to the body center but heating is caused by eddy currents in lossy tissue that depend on tissue type and geometry of the induction coils and tissue load.[123] Heating may be concentrated deep in the body around implanted ferromagnetic seeds or particles that couple into the external magnetic field more effectively than surrounding tissue. Without insertion of ferromagnetic material into the body, the distribution of power deposition in tissue directly from induced eddy currents is not adjustable. By inserting ferromagnetic seeds or particles in the tumor, the distribution

Figure 21-5 Example of a commercial microwave waveguide applicator heating system for superficial hyperthermia treatments. Typical systems operate at 915 MHz or 430 MHz for heating 2-4 cm depth. Energy is usually coupled into tissue through a thin layer of deionized water, which is temperature controlled to maintain the skin surface below 44°C. A single waveguide applicator provides no control of power distribution in the x-y plane, aside from what can be achieved by physically moving the applicator. The arrow indicates the aperture of the waveguide. The water bolus would be attached to the waveguide in this location.

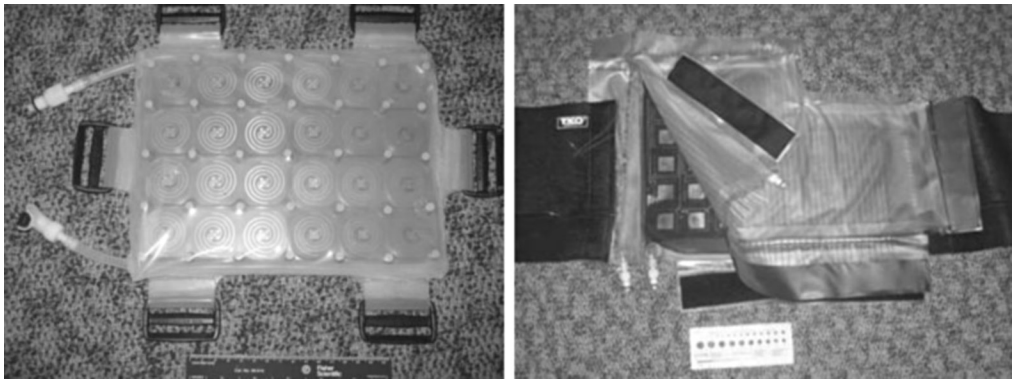

Figure 21-6 Two examples of thin and flexible microstrip antenna array applicators currently under development for superficial hyperthermia. A <1 cm thick temperature controlled deionized water bolus is used to couple microwaves into tissue and maintain the skin surface below 44°C. These conformal array applicators are driven with 8 or more microwave power sources to provide adjustment of the power distribution across the tissue surface.

of heating may be adjusted by changing the density of implanted material. There has been a resurgence of interest in ferromagnetic materials for hyperthermia. See recent special edition of the International Journal of Hyperthermia for more details.[123]

Capacitive Heating

Capacitive heating uses radiofrequency fields between 5 and 30 MHz to generate electric current between two or more conductive electrodes. Heating tends to be concentrated nearest the electrodes, but temperature-controlled saline boluses are used to reduce hot spots on the skin surface and help cool superficial fat.[124] Using different size electrodes, the maximum power deposition may be shifted toward the smaller electrode. This technique can be used with large electrodes on the skin[125,126] and one or more small intracavitary electrodes such as a balloon electrode for esophageal tumors.[127] The thickness of the superficial fat layer is a significant factor for this method because of extra heating in high resistance fat tissue relative to deeper lying high conductivity soft tissues. To date, RF capacitive heating has been used most widely in Asia, where patients tend to be thinner.

Radiofrequency Phased Array

The third option for heating with electromagnetic fields is the radiofrequency phased array.[128-131] These devices consist of an array of RF antennas arranged in a geometric pattern surrounding the target body region. Antennas are driven with multiple independently controllable power amplifiers but using a common radiofrequency source, allowing phase addition fields from all antennas to add together to form a heat focus in the center of the array. The focus can be shifted off center and around the tumor by variation of relative phase of the drive signals from each amplifier. For a multiple antenna phased array deeper power deposition into tissue is possible than using several independent antennas without phase addition. The phased array technique has more flexibility for controlling power deposition pattern than direct tissue magnetic induction and capacitive techniques which are altered significantly by heterogeneous tissue properties and few power control variables. Figure 21-7 shows one example of a 12 antenna annular phased array applicator mounted on the patient table of a magnetic resonance imaging (MRI) system. This MR compatible 100 MHz RF phased array applicator fits inside the bore of 1.5 T magnet allowing MR imaging of temperature to rise inside the body during hyperthermia treatment.

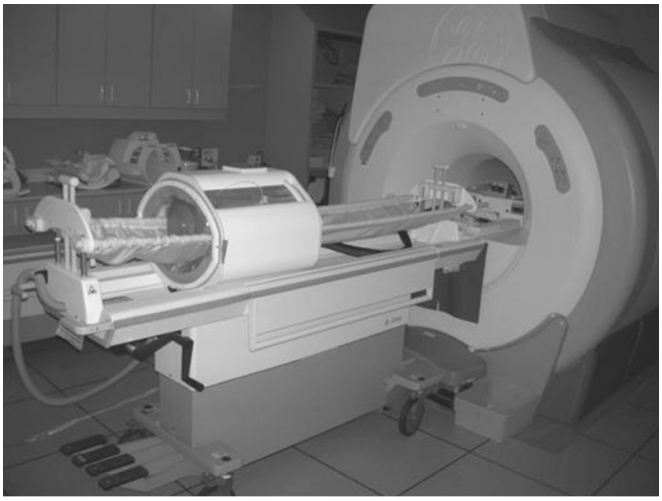

Figure 21-7 Example of 12 antenna radiofrequency phased array applicator for deep regional hyperthermia treatments. This array is driven at 100 MHz and has appropriate filtering to enable use inside a magnetic resonance (MR) imaging system for monitoring deep tissue temperatures with proton resonance frequency shift based MR thermal imaging. The large focus of heating inside the phased array applicator may be guided into the tumor by adjusting phase and amplitude of the 12 antennas, in response to real-time feedback from the MR thermal images.

Ultrasound Heating

Energy transfer from an ultrasound acoustic pressure field results from viscous friction within the tissue caused by successive compression and expansion from the high and low pressure wavefront. As with electromagnetic sources, heating falls off exponentially with distance from a single source, and penetration of the ultrasound field decreases with increasing frequency. However, because the wavelength of an US field is several orders of magnitude smaller than that of EM fields, and on the order of mm, ultrasound energy may be focused into small volumes deep in the body, given sufficient number of transducers to spread out the surface power density over a large surface. In practice, it is anatomic geometry and tissue heterogeneity (air reflects and bone preferentially absorbs ultrasound) that restrict the utility of US for heating large tumor volumes at depth. The availability of an adequate "acoustic window" (a path unobstructed by bone or air proximal and distal to the target) is the primary concern in clinical HT with ultrasound, wherein the entry window and acoustic gain to the target determines the maximum size and depth of the target volume.

Energy is coupled into tissue using temperature-controlled degassed water. Single and multiple transducer unfocussed devices have been designed for superficial tumor (2-5 cm) heating which typically operate in the 1-5 MHz range.[132-135] Deep heating with ultrasound is accomplished by using electrically or mechanically scanned focused transducers, phased arrays, or multiple scanned focused transducers, normally in the 0.5 to 2 MHz range.[135]

High intensity focused ultrasound systems are now available with high density multiple transducer arrays that are integrated into magnetic resonance imaging systems for simultaneous anatomic imaging, real-time thermal monitoring and beam steering control, and immediate post treatment assessment of ablation volumes. These systems produce a tight focus inside the cranium[136] or torso,[137] and are used most often for high temperature thermal ablation treatments.[139] For some treatment sites, additional localization is obtained using transducer arrays implanted in interstitial or intracavitary catheters. Excellent reviews of the physics and clinical aspects of focused ultrasound therapy have been published.[138-141] Focused ultrasound has also been tested extensively for its potential to augment nanoparticle delivery. This includes applications to open the blood brain barrier.[142-145]

Measurement of Temperatures during Hyperthermia

Invasive Thermometry

Invasive thermometry is the current standard for most hyperthermia treatments, involves physically placing thermometry probes into the tumor within implanted needles or catheters to read subsurface temperatures.[146-148] Although the accuracy of invasive thermometers is sufficiently precise (typically ± 0.3°C) to resolve important differences in thermal dose (as described earlier), this type of thermometry has many disadvantages. Disadvantages include discomfort to the patient and

risk of hemorrhage and/or infection, the expense of physician time required for catheter placement, and necessity for imaging to verify placement of thermometers in the target volume. In addition, the sparse nature of the data obtained makes it difficult to spatially control power deposition or alter treatment to improve temperature distributions.[149,150] The most common method for doing invasive thermometry is to insert blind ended catheters into a tumor, using either ultrasound or CT guidance.[147] Alternatively, for deep-seated tumors, thermometers may be placed inside orifices that are surrounded by tumor, such as the rectum, urethra, bladder, or cervix.[151] The probes can be multipoint sensors that remain fixed in place, or sensors are moved cyclically during treatment to record temperatures at many points along the catheter. There are guidelines published for how these measurements should be taken for all HT devices.[147,151-154] In spite of its sparse nature, invasive thermometry can provide valuable information about the quality of a treatment. A number of clinical reports have correlated temperature-related parameters to clinical response.[67,155-160]

Noninvasive Thermometry

Noninvasive thermometry is emerging in answer to the critical need for volumetric thermometry to visualize complete 3D temperature distributions in real time during deep hyperthermia treatments. In typical treatments using radiofrequency phased array applicators monitored only by invasive probes the number of thermal monitoring points is insufficient to adequately characterize the heating pattern. Parts of the tumor are unheated whereas too much heat is sometimes generated in surrounding normal tissues. Similarly, multiple element array superficial hyperthermia applicators require more temperature measurements than are possible with a limited number of invasive probes to monitor and control all independently powered heat sources. Insertion of multiple interstitial probes is clinically impractical. For superficial tumors (<1.5 cm depth), thermal dosimetry is often limited to probes placed in fixed positions on the skin or mapped through catheters lying on the skin to characterize the distribution of heating across large area disease as a prediction of subsurface temperatures.

To address the shortcomings of invasive thermometry, a number of noninvasive techniques are under investigation. Infrared thermography has been available for years for monitoring surface temperature distributions.[161] Although spatial resolution and accuracy are excellent, the method requires open access to visualize the surface so is not compatible with most heating technologies. A new approach for monitoring 2D surface temperature distributions even when the surface is buried under a water-bolus coupled applicator involves use of high density arrays of fiberoptic sensors mounted in a large surface-conforming Thermal Monitoring Sheet (TMS).[162,163] Other noninvasive thermometry approaches under development include electrical impedance tomography (EIT) sometimes called applied potential tomography,[164-165] ultrasonic temperature imaging using change in backscattered energy,[166-167] electron paramagnetic resonance (EPR),[168] active microwave imaging or tomography,[169] microwave radiometry,[170-176] and real-time multislice magnetic resonance thermal imaging (MRTI).

While there are clinical applications for each of these technologies, MRTI is being studied most intensively for volumetric characterization of temperature distributions and control of radiofrequency beam steering for deep tissue hyperthermia. Although several MR tissue parameters are sensitive to changes in temperature, attention has focused on investigation of the change in water proton resonance frequency shift (PRFS),[138,177-179] even in tissues with low water content like breast.[180,181] Use of noninvasive MR thermometry should translate into improved treatment efficacy by providing quantitative volumetric thermal dosimetry in real-time to assist the delivery of improved quality HT treatments. Figure 21-8 shows an example of non-invasive thermometry with MRTI during heat treatment of a lower leg sarcoma with a four antenna 140 MHz mini annular phased array applicator. The method has yielded a temperature resolution of better than 1.0°C compared with calibrated with invasive sensors in human patients.[182] Moreover, MR imaging offers opportunities for validation of treatment planning systems,[183-185] dynamic control of treatment delivery,[186-189] and posttreatment assessment of tissue damage.[190] The use of MRTI has been increasing rapidly in recent years for clinical applications in both moderate temperature hyperthermia and high temperature thermal ablation therapy such as radiofrequency, laser, and high intensity focused ultrasound.[191] The International Journal of Hyperthermia summarized the status of MR thermometry in a

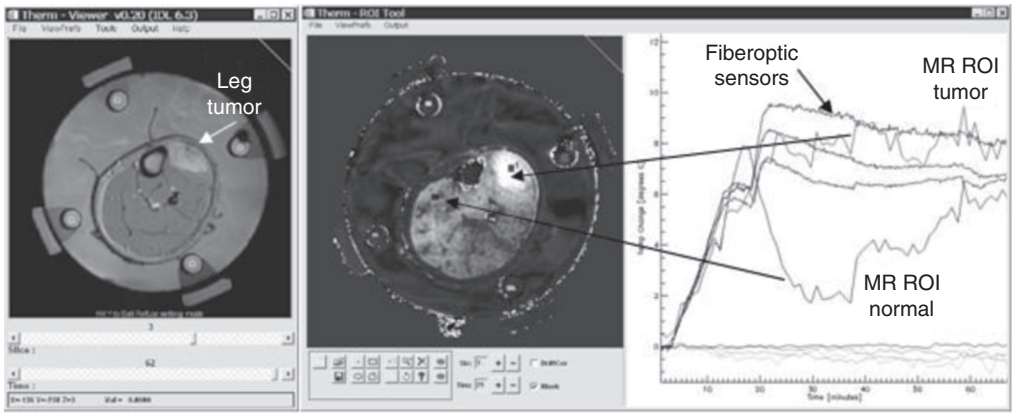

Figure 21-8 Real-time display during MR monitoring of heat treatment. Left panel shows anatomical image of leg in 24 cm diameter phased array applicator. The central image shows a typical differential temperature image display at about 20 minutes into heat treatment, after the phase of the four 140 MHz twin dipole heating antennas had been adjusted to move the heat focus into the tumor at upper right of leg. The PRFS calculated temperature rise is displayed on the same plot as invasive fiberoptic sensors in the tumor. The dramatic refocusing of power deposition at 18 minutes into treatment is seen to shift heating away from normal tissues in upper left of image and into the tumor at upper right, as indicated qualitatively by the brightness of the temperature image and quantitatively in the calculated temperature rise for tumor in the plot at right.

special issue.[192]; additional background can be found in review articles by Rieke and Butts[193] and MacFall and Soher.[178]

In a paper by Craciunescu et al[182] the critical steps were presented to attain rapid volumetric real-time image-guided hyperthermia treatments. With update times of the order of minutes, the claim of real-time treatment control agrees with an accepted definition of "real-time" given for thermal therapies by Rieke and Butts,[193] as "an update time that is small compared to significant changes in temperatures during treatment." This update time is different in hyperthermia applications (minutes or more) versus ablation therapies (a few seconds to minutes). This whole process lends credibility to the idea that future hyperthermia systems will use image feedback to control beam steering and focus heating in tumor targets.

CLINICAL HYPERTHERMIA

General Considerations

HT Alone

HT alone has been studied in the treatment of superficial tumors. While an occasional response is noted, the duration is typically quite short.[194,195] No long-term tumor control has been described with the use of HT as a sole treatment modality. HT alone remains widely practiced in certain alternative and complementary medicine clinics. Its use, however, is not supported by any peer-reviewed published scientific data.

Thermal Ablation

In contrast to effects of mild to moderate temperature hyperthermia, thermal ablation can yield durable long-term results. A meta-analysis was conducted of four phase III trials (766 patients) comparing percutaneous ethanol injection to radiofrequency ablation (RFA) for patients with liver metastases. Survival and local control rates were superior for RFA with a hazard ratio of 0.66 for survival.[196] However, the complication rate and costs of application were higher for RFA. RFA is generally used when patients are not suitable surgical candidates.[196-199]

HT with Radiotherapy

A large number of reports attest to the efficacy of HT in combination with radiotherapy (RT). The majority of publications have been from phase II trials involving patients with superficial malignancies (and thus more amenable to heating) as a component of more generalized disease, such as local recurrence of breast carcinoma on the chest wall. With the addition of HT to radiation, clinical response rates have approximately doubled from 25% to 35% with radiation alone to 50% to 70% with RT + HT.[200] In addition to phase II studies, several phase III trials have now been conducted worldwide with approximately two-thirds published in the English literature. These trials generally have been positive, lending additional validity to the information obtained from phase II studies.

HT with Chemotherapy

Published data on the efficacy of locoregional HT in conjunction with chemotherapy (CT) is much less frequent. Both animal and human data have been reviewed.[200] Particularly encouraging phase II results were reported for sarcomas,[201] which led to a recently completed phase III trial (see section on phase III trials for outcomes on the sarcoma trial and a small esophageal cancer trial).

Wessalowski et al recently reported results of a phase II study, conducted on 44 children ranging in age from 7 months to 16 years who had refractory or recurrent germ cell tumors.[202] All of these patients had received cisplatin previously as part of their initial treatment. They were treated with a combination of cisplatin, etoposide, and ifosphamide, where HT was given twice weekly in three cycles. The objective response rates were similar to what is expected from front line therapy. The 5-year overall survival rate was 62%. The results were better than anticipated given the likelihood that the majority had drug resistant tumors. As discussed earlier, hyperthermia reverses drug resistance. This effect may have played a role in the overall success of the trial.

Trimodality Therapies with HT, RT, and CT

A small randomized phase III trial involving patients with esophageal cancer showed a higher pathologic CR rate when HT was added to chemoradiotherapy compared with chemoradiotherapy alone.[203] More recently, the combination of HT + cisplatin + radiotherapy has been evaluated in patients with locally advanced cervix cancer. Twelve patients were treated in this series, with local control being achieved in ten. The two patients with local failure presented with local recurrence following hysterectomy.[204] In a follow-up report, Westermann et al combined results of this trial (with longer follow-up) with results from several other institutions that had conducted similar studies.[205] A total of 68 patients were included in the analysis. Of these, 61 achieved a complete response. At a median follow up of 538 days, 74% of patients were disease free. This is a favorable outcome, compared with historical controls. To date, however, a confirmatory phase III trial has not been reported.

The combination of 5FU, HT, and radiation therapy yielded favorable responses in patients with locally advanced colorectal cancer in a phase II study.[206] In a retrospective study comparing sphincter sparing in patients with locally advanced rectal cancer, those who received HT in addition to RT and chemotherapy tended to have a higher sphincter preservation rate, compared with those who were treated with radiochemotherapy.[207] To date, no phase III trials have been reported comparing the addition of HT to chemoradiotherapy for locally advanced rectal cancer.

Normal Tissue Damage from HT

HT does not significantly increase early or late toxicity of radiation.[67-69] The most common toxicities of HT are superficial or subcutaneous tissue burns. They are usually first or second degree and small in volume. Such burns occur in approximately 5% of patients treated in the Duke experience; characteristically they do not exceed 3 to 4 cm in maximum diameter. Third-degree burns are infrequently observed (<1% incidence). Complications from thermometry catheters are infrequent if the catheters are removed following each HT treatment.[208] When catheters are left in place throughout the course of HT (e.g., for several weeks), the frequency of complications rises significantly, particularly secondary infections.[209]

There are potential medical contraindications to deep-regional HT related to the physiological stress. Guidelines for patient selection for deep hyperthermia have been developed.[154,211]

Relationship between Thermal Dose and Outcome

Quality assurance for delivery and measurement of temperatures during hyperthermia are essential to identify quantifiable thermal dose parameters. Negative phase III clinical trials conducted by the RTOG in the 1980s were attributed to this issue.[212-214] Quality assurance standards as well as data acquisition procedures were subsequently established by both the

The maximum size that one can ablate in a single session is <5 cm. Recurrence at the margin can occur, which may require additional treatments. Feasibility of performing ablation can be affected by proximity of the lesion to thermally significant vessels[199] or other key structures that should be avoided (e.g., diaphragm, bile ducts). The FDA has granted 510K approval for three commercial RFA devices. High intensity focused ultrasound can also be used for thermal ablation. The FDA recently approved one system for use in treatment of painful bone metastases. The approval is specifically for patients in whom radiotherapy is not an option <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm327521.htm>.

RTOG[147] and European Society of Hyperthermic Oncology (ESHO).[210,211,215] The biological underpinning for thermal dosimetry was discussed previously in the biology section of this chapter.

Dosimetry for hyperthermia is distinctly different from that for radiation therapy in that the amount of energy deposited does not correlate with the degree of damage. This is because damage is related to the amount of temperature rise and the time of exposure, both of which are governed by the net balance between how much energy is deposited vs. how much is carried away by thermal conduction and perfusion. In the case of hyperthermia, the dosimetric unit used most often has been one that was derived empirically from evaluation of the Arrhenius relationship for cell killing in vitro as well as from numerous studies of degree of tissue damage as a function of temperature and time of exposure.[1] As was described in detail previously, the unit most often used has been equivalent minutes at 43°C (CEM 43°C). Application of this concept to the clinic, however, requires integration of non-uniform temperature history data with CEM43°C.

Since temperatures during hyperthermia treatment are non-uniform, it is necessary to derive descriptive parameters from the temperature distribution to which the CEM43°C parameter can be applied. A number of clinical parameters have been described based on simple descriptions of the multipoint thermometry, such as minimum temperature, average temperature, etc. Parameters that have proven useful for describing temperature distributions are the 10th percentile of the temperature distribution, which is commonly referred to as the T_{90} (90% of measured points exceed this value) or the T_{50}, which is the median temperature. Use of these types of parameters leads to dosimetry that is comparable across patients and studies, as long as quality assurance guidelines are followed with respect to the placement and number of thermometers used. The resultant units are referred to as CEM43°CT_{90} or CEM43°CT_{50}.

Retrospective evaluation of many phase II and phase III trial results have shown positive relationships between measures of thermal dose and treatment outcome, suggesting that higher thermal doses will yield better responses when HT is combined with radiotherapy.[156,158-160] In all positive studies reported to date, thermal analysis was performed retrospectively. It has been more difficult to correlate variations in thermal dose administered a priori and clinical outcome. Two studies compared various numbers of heat treatments given in combination with fractionated RT,[216,217] using the assumption that more treatments would yield greater cumulative thermal dose. Neither study showed any benefit with higher numbers of HT fractions, which could in part be due to the fact that there was considerable overlap in thermal doses between the treatment arms. This is because temperature is a stronger determinant of thermal dose than time-at-temperature (see biology section previously). A canine study compared radiation therapy combined with whole body HT + local HT compared with local HT alone. The CEM43°CT_{90} was higher in the group that received whole body hyperthermia, but there was no difference in duration of local control between the two treatment arms.[218] One potential explanation for the lack of improvement in local control might have been the induction of thermotolerance during the whole body HT, which was administered prior to application of local heating.

The first attempt to prospectively control thermal dose, as prescribed by the CEM43°CT_{90}, was a study of preoperative RT + HT for soft tissue sarcomas.[59] The outcome variable was pCR assessed at the time of surgery, and the percentage of patients predicted to achieve a pCR as a result of achieving CEM43T_{90} > 10 minutes was predicted to be 75%, based on prior phase II studies.[158] The pCR rate in this study was 54%, which was below the 95% confidence level for the projected rate. A number of explanations are possible for failing to achieve the projected pCR rate, including the sparseness of the temperature information gained. Recently, it was reported that other mitigating physiologic factors may have confounded the results of this study.[219]

Two additional phase III trials have been completed by the same group—one in patients with superficial tumors and the other in pet dogs with soft tissue sarcomas. In both of these trials there was clear separation in thermal doses between the two treatment arms.[156,220] Most importantly, improved response and duration of local control was observed in the groups that prospectively received the higher thermal dose. These are the first two and only trials conducted in which prospective control of thermal dose has yielded demonstrated improvement in local tumor response and/or control. They clearly indicate that better prospective control of thermal dose may ultimately lead to methods to truly optimize hyperthermia treatment. A recent study by this same group evaluated the question of how many fractions of HT (1 vs. 4 fractions/week) should be delivered in conjunction with fractionated RT.[46] The cumulative thermal dose was kept equal between the two arms. In prior clinical trials, the number of hyperthermia treatments has been restricted to no more than 2/week, because of concerns about persistence of thermotolerance between HT fractions. However, heat radiosensitization is not affected by thermotolerance, thus it was reasoned that giving 4 fractions of HT/week might yield superior results to giving 1 fraction/week. Surprisingly, giving 1 fraction/week was significantly better than 4, based on tumor response at the end of therapy.

Phase III Clinical Trials Overview – HT + RT

Phase III trials have involved a wide variety of diseases, including superficial malignancies and tumors deep within the body. Trials have been conducted with either palliative or curative intent. A summary of the most important of these trials is presented in Table 21-2.

Breast Cancer

Chest wall recurrences of breast cancer are difficult to control with conventional approaches, and many patients develop such recurrences despite prior adjuvant radiotherapy or systemic therapy. Since they are superficial tumors, they have been amenable to HT trials. Five separate phase III trials were combined for analysis in an international collaborative study by Vernon et al.[221] Patients were randomized to either RT alone or RT with HT. Treatment was prescribed according to ESHO and RTOG guidelines. HT techniques differed somewhat between institutions but are well documented, as is information concerning temperature distributions and thermal dosimetry.[160] Overall, the five trials demonstrated a significant improvement in the complete response rate for patients receiving HT + RT (59%) compared with RT alone (41%), with an odds ratio of 2.3 (95% CI 1.4-3.8) (see Table 21-2). The greatest effect was observed in patients with recurrent lesions in previously irradiated areas where further irradiation was of necessity limited to low doses. No survival advantage was seen.

Other Superficial Malignancies

A study was conducted by the RTOG in the 1980s comparing RT alone with RT + HT in superficial measurable tumors (RTOG 8104).[213,214] Three hundred seven patients were included in the study; approximately half of the patients had head and neck tumors, one-third had breast carcinoma (chest wall recurrences), and the remaining had a variety of superficial malignancies. Patients treated with RT + HT had a

TABLE 21-2 Key Phase III Trials: Hyperthermia Combined with Radiotherapy

Author	Tumor Type/ Location	Type of Trial	N	RX Arm: RT	RX Arm: RT + HT	RT Dose (Gy)	# Fx	Mean Tx Time	Hyperthermia: # Fx	Hyperthermia: Thermal Dose Goals/ reported data	End Points: Control Arm (RT)	End Points: Treatment Arm (RT + HT)	Significance ($p < 0.05$)
van der Zee[227]	Pelvic*	Dutch multicenter	358	176	182	—	—	—	1/wk, ≤5 Fx (1-4 hr post RT	Target = 60 min @ 42C; avg total HT, 90 min	CR 39% (3 mo) 3-y OS 24% 3-y LC 26%	CR 55% (3 mo.) 3-y OS 30% 3-y LC 38%	Yes Yes Yes
	Cervix subgroup	Dutch multicenter	114	56	58	≥42	23-28	48 d	Same	Same	CR 57% (3 mo) 3-y OS 27% 3-y LC 41%	CR 83% (3 mo.) 3-y OS 51% 3-y LC 61%	Yes Yes Yes
Sneed[226]	GBM (after RT)	Single institution	68	33	35	59.4 Gy EBRT + BT 60 Gy	33 1	32 d 100 hr	2Fx (pre-post BT)	Median CEM 43°T90: 14.1 Median CEM 43°T50: 74.6	TTP, median 33 weeks TTLTP 35 wks 2-y OS 15%	TTP, median 49 weeks TTLTP 57 wks 2-y OS 31%	Yes Yes Yes
Emami[212]	Various (HN, pelvis, other)†	RTOG multicenter	173	87	86	Prior + BT study dose <100 Gy	—	1 d (BT)	1-2 pre or post BT	Goal: Tmin 43° C for 60 min	CR 54% 2-y LC 37% 2-y OS 29%	CR 57% 2-y LC 43% 2-y OS 36%	No No NR
Vernon[221]	Breast	Multicenter	306	135	171	29-50 Gy +/– boost	Varied	2-5 wks	1 to 8	Goal: T > 42.5°C Q 30 min	CR 41% 2-yr OS 40%	CR 59% 2-yr OS 40%	Yes No
Overgaard[57]	Melanoma	Multicenter 70 pts, 134 sites	68	65	63	24-27	3	8 d	3	Goal: 43°C Q 60 min	CR 35% 3 mo 5-y LC 28%	CR 62% 3 mo 5-y LC 46%‡	Yes Yes
Kitamura[225]	Esophagus	Single institution	66	34*	32*	30 Gy	13	3 wks	6	42.5–44.0° C Q 30 min	Downstg, 44% CR 8% 3-y OS 24%	Downstg, 69% CR 26% 3-y OS 50%	Yes Yes NR
Valdagni[223,224]	Head and neck nodes	—	41	21/22 nodes	16/18 nodes	64-70 Gy	NR	30 d	2 vs 6 Fx	Goal: Tmin + 42.5°C Q 30 min	5-yr LC 24% 5-y OS 0%	5-yr LC 69% 5-y OS 53%	Yes Yes
Perez[214]	Misc. superficial	RTOG 8104 multicenter	307	117	119	32 Gy	8	4 wks	8	Goal: 42.5°C Q 60 min BIW	CR total 30% CR for lesions <3 cm 25%	CR total 32% CR for lesions <3 cm 52%	No No
Datta[222]	Head and neck	Single institution	65	32	33	50 Gy + boost	25	5 wks	BIW	Goal: 20 min @ 42.5°C	CR 31% @ 8 wk	CR 55% @ 8 wk§	Yes

Wks, *Weeks;* d, *days;* Q, *every;* hr, *hour;* RX, *treatment;* RT, *radiation;* Fx, *fractions;* HT, *hyperthermia;* CT, *chemotherapy;* CR, *complete response;* 3-y, *3-year;* downstg, *downstage;* LC, *local control;* OS, *overall survival;* DFS, *disease-free survival;* FU, *follow-up;* HN, *head and neck;* TTP, *time to progression;* TTLTP, *time to local tumor progression;* Rec, *recurrent;* GBM, *Glioblastoma multiforme.*

**Rectal and bladder subgroup data (non-significant difference in outcomes).*

†HN and pelvic subgroup date (no significant difference in outcomes).

‡RR (RT + HT vs RT alone): CR = 4.01; 2 yr local control = 1.73.

§DFS, no difference total gp but advantage to RT + HT for Stage III-IV pts.

complete response rate of 32% compared with 30% for those receiving RT alone. Subgroup analysis revealed significant improvements in duration of local control only in patients with tumors less than 3 cm in depth and in those with breast and/or chest wall recurrences. It was postulated that the better outcome in smaller tumors was a consequence of better heating. This trial was plagued by highly variable heating techniques and crude thermal dosimetry. These problems led to the development of subsequent RTOG guidelines for performing HT.[147]

Head and Neck Cancer

There are two randomized series demonstrating an advantage to HT combined with RT (see Table 21-2). The first study by Datta et al randomized 65 patients to radiation alone vs. RT and HT.[222] RT doses consisted of 50 Gy in 5 weeks to the primary site and regional lymphatics followed by 10 to 15 Gy given to sites of gross disease in daily fractions of 2 Gy. HT was given twice a week with 72 hours between each session. The HT + RT arm showed significant improvement in response in patients with stage III and IV disease. For example, patients with stage III disease receiving combined treatment had a 58% CR compared with 20% in the RT alone group. There was no benefit for patients with stage I and II disease, with greater than 90% of these patients achieving a CR with either treatment. This trial from India evaluated both the primary site as well as neck nodes, despite the recognized difficulties of effectively delivering heat to most primary head and neck tumors.

A second trial from Italy by Valdagni et al restricted treatment and evaluation to metastatic cervical lymph nodes. This study randomized 41 patients with advanced local regional squamous cell carcinoma of the head and neck to treatment with either RT alone or RT combined with HT.[223,224] Long-term follow-up allowed for analysis of response, duration of local control, and survival. The five-year actuarial local control in the neck with RT alone vs RT + HT was 24 vs 69%, and 5-yr OS was 0 vs. 53%; all of these differences were statistically significant. There was no clear enhancement of toxicity or any clear relationship between thermal dose received and outcome. Nonetheless, this well-executed and described phase III trial, despite the relatively small number of patients, is an important component of the evidence suggesting the value of HT.

A trial of interstitial hyperthermia was carried out primarily in head and neck patients by the RTOG.[212] This trial entered 173 patients with persistent or recurrent tumors after prior radiotherapy and/or surgery that were amenable to interstitial radiotherapy. The lesion site was the head and neck in approximately 45% of patients, the pelvis in approximately 40%, with miscellaneous sites accounting for the rest. The patients were randomized to receive interstitial RT alone ± interstitial HT. Overall there was no difference in complete response rates or 2-year survival. There were major quality assurance issues with this trial. Only one patient in the entire group was considered to have had adequate HT. This trial, as well as the previously mentioned RTOG trial, provided impetus for the subsequent development of HT guidelines by the RTOG.[153]

Esophagus Cancer

Two randomized studies demonstrated an advantage to the addition of HT to chemoradiotherapy or chemotherapy alone in the neoadjuvant treatment of esophagus cancer. In the first study by Kitamura et al 66 patients with squamous cell carcinoma of the thoracic esophagus were randomized to preoperative HT, RT, and CT, compared with chemoradiotherapy alone.[225] The chemotherapy (bleomycin) and HT were given concurrently 1 hour prior to the radiation in a 3-week regimen with a total RT dose of approximately 32 Gy. Clinical complete responses and pathologic responses were significantly improved in the tri-modality arm, with a pathologic CR of 26% combined in the tri-modality group vs. 8% in the chemoradiotherapy group (see Table 21-2).

In a follow-up study, an additional 40 patients were treated with chemotherapy alone (bleomycin and cisplatin) or combined with HT.[225] No RT was given in this trial. Again, an improvement in histopathologic response was noted favoring the HT group (19% vs. 41%).

Malignant Melanoma

A major multicenter trial was conducted in patients with metastatic melanoma by Overgaard et al.[57] Seventy patients with 134 metastatic or recurrent malignant melanoma lesions were randomized to receive RT ± HT. Overall there was a significant benefit for the addition of HT with a 2-year local control of 46% in the combined group compared with 28% for those receiving RT alone (see Table 21-2). Quality assurance issues were problematic in this trial, with only 14% of treatments achieving the protocol objective of 43°C for 60 minutes. Despite this, positive benefits were seen.

Glioblastoma Multiforme

A University of California San Francisco study by Sneed et al evaluated interstitial HT combined with a brachytherapy boost for selected patients with glioblastoma multiforme.[226] One hundred twelve patients were entered into this trial, which randomized patients whose tumor was implantable following external beam RT and chemotherapy to receive brachytherapy ± HT. Seventy-nine were randomized; 33 patients were dropped from the protocol due to disease progression. Both time to tumor progression and survival were significantly improved for the HT patients compared with those treated with brachytherapy alone (see Table 21-2). Two year survivals in the two groups were 31% and 15%, respectively. Toxicity appeared to be slightly greater in the HT patients, with seven grade 3 toxicities reported compared with one in the brachytherapy alone group. Thermal dose data showed that good heating was achieved in most patients. No significant correlation was seen between thermal dose and response.

Pelvic Tumors (Cervix, Bladder, Colorectum)

The Dutch hyperthermia group conducted a study by Van der Zee et al in which 358 patients with previously untreated locally advanced pelvic tumors were randomized to receive RT alone or RT + HT (see Table 21-2).[227] HT treatments were given once weekly for a total of five treatments. Generally, thermal goals were not achieved, but detailed thermal dose analyses have not been published. There were approximately equal numbers of patients with bladder, colorectal, and cervical carcinomas. Complete response rates were 39% and 55% after RT alone and RT + HT, respectively ($p \leq 0.001$). Duration of local control was also significantly improved with RT + HT. Patients with cervical carcinoma benefited the most. Three year survivals were 27% and 51% in the RT and RT + HT groups, respectively ($p = 0.003$). This study has been criticized for suboptimal therapy in the control arm, namely RT alone as opposed to the combination of RT + CT. At the time the trial was initiated in 1990, the role of chemotherapy in cervix carcinoma was not established. Subsequently, a number of studies published in 1999/2000 have demonstrated a survival advantage for concurrent cisplatin-based chemotherapy in cervical carcinoma.[228-232] Additional phase III trials are needed to establish whether there is an advantage to thermochemoradiotherapy compared with chemoradiotherapy for locally advanced cervix cancer.

TABLE 21-3 Key Phase III Trials: Hyperthermia Combined With Chemotherapy

Author	Tumor type	Trial	No. Pts	Therapy	# cycles	Thermal Dose Goals/ reported data	END POINTS
Colombo[234,235]	Rec or primary bladder	Multicenter	83	Mitomycin C	8 weekly + 4 monthly	42 +/– 0.2°C Q 1 hour	23/41 relapses,control arm vs 6/42, combined arm
Issels[233]	Locally advanced STS	EORTC Multicenter	341*	Etoposide, ifosfamide, doxorubicin; optional postop RT*	4 cycles before and after local therapy	42°C 60 minutes Q 1 hour	Local progression*, median 34 mo FU: CT + HT 56/169; CT, 76/172

Postop RT, *Postoperative irradiation;* HT, *hyperthermia;* CT, *chemotherapy;* STS, *soft tissue sarcoma (extremity, retroperitoneal).*
**125 of 339 evaluable patients did not receive postop RT as a component of local therapy.*

Phase III Clinical Trials Overview – HT + CT

Soft Tissue Sarcoma

The EORTC recently reported on results of a phase III trial by Issels et al that compared neoadjuvant thermochemotherapy to chemotherapy (etoposide, ifosfamide and doxorubicin; Table 21-3).[233] A total of 341 patients were enrolled. Patients received four cycles of neoadjuvant treatment before receiving definitive surgery and/or radiotherapy for the primary tumor. The hazard ratio for local PFS, the primary outcome variable, was 0.58 for patients receiving thermochemotherapy (p = 0.003). At 2-year follow-up, the combined arm had a 15% higher rate of PFS. DFS analysis showed a hazard ratio for the combined arm of 0.7 (p = 0.011). For those patients who completed the combined arm treatment, the hazard ratio for OS was 0.66 (p = 0.038).

Bladder Cancer

Colombo et al conducted a randomized phase III trial for recurrent superficial bladder cancer, which utilized intravesicular mitomycin C with and without bladder HT, using an intravesicularly placed microwave antenna to heat the bladder contents and wall (see Table 21-3).[234] A large majority of these patients had already failed mitomycin C previously. Eighty-six patients were enrolled and 75 completed therapy and were evaluable. Treatment of the bladder commenced after surgical removal of the tumor. The hazard ratio for local control after chemotherapy alone vs. thermochemotherapy was 4.8 (p = 0.0002). The heated group had a higher rate of complications, particularly related to thermal damage to the posterior bladder wall. Most of this damage resolved quickly, with only one patient experiencing a prolonged several month recovery period. Long term follow-up data from this trial has recently been reported (88% of patients in prior trial available).[235] The 10 year disease free survival rates were 53 and 15%, in favor of the addition of HT to mitomycin C (p = 0.001). Bladder preservation rates were comparable between the two arms.

There has been increasing interest in using HT for treatment of non-muscle invasive bladder cancer, as a result of the Colombo trial.[236-239] A recently completed pilot trial using the BSD2000 to heat the bladder noninvasively, in combination with mitomycin C, demonstrated that this approach was feasible and well tolerated.[240] This may prove to be an effective alternative approach to the intravesicular microwave antenna used by Colombo.

Summary of Clinical Trials

Results of the published phase III trials above are intriguing. Apart from the RTOG trials, they all appear to demonstrate substantial benefits with the addition of HT to RT or HT with chemotherapy. However, several of the trials were associated with significant design and implementation problems, including relatively small numbers of patients, thermal dosimetry information that was highly variable in nature, thermal goals that were often not achieved, and control arms that may not have represented optimal standard therapy. Despite these difficulties, the positive clinical outcome of these trials and the sound scientific rationale for adjuvant hyperthermia justify continued efforts in technological refinements and the conduct of well-designed clinical trials.

CHALLENGES/CONTROVERSIES/ FUTURE POSSIBILITIES

There are significant challenges to the continued development of hyperthermia. These can be roughly categorized into three types: (1) improvements are needed to make the treatment less technically challenging, (2) widespread establishment of chemo-radiation for many locally advanced cancers have reduced the potential population of patients who could benefit from thermoradiotherapy, and (3) emphasis on development of targeted therapies, such as tyrosine kinase inhibitors and anti-angiogenic drugs, which show promise for selective targeting of tumors while greatly minimizing normal tissue toxicities are easier to implement than HT. It is important to consider how hyperthermia can fit into this rapidly changing landscape of oncology research and practice and this is discussed next.

Technical Challenges

The FDA recently approved the use of deep heating with the BSD-2000, in combination with radiotherapy, to treat women with recurrent cervix cancer, where chemotherapy is not an option <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm286404.htm>. Aside from this orphan designation, the use of hyperthermia for deep-seated tumors is still experimental in the United States. In Europe, deep hyperthermia has been more widely accepted and is approved in The Netherlands, Germany, and Italy as an adjunct therapy with radiotherapy and chemotherapy. Regardless of whether it is approved or not, it is technically challenging and expensive to administer, because it requires time of a dedicated team involving highly skilled physicists, engineers, physicians, and nurses to perform it safely and accurately. Invasive thermometry requires dedicated physician time to place thermometry catheters, and imaging is

needed to document thermometry placement. Currently, control of applied power requires significant technical skill and experience. These issues place important constraints on the promulgation of hyperthermia to the broader medical community. Progress will continue to be impeded until the technology is made more user-friendly. Advances in noninvasive thermometry, as discussed above, hold great promise for reducing the burdens associated with invasive temperature measurements.

Thermal Dose Prescription

Even if noninvasive thermometry were available, until recently there has been no information on what target temperature ranges are needed to optimize this therapy. Such information is the second key for providing a quantitative assessment of hyperthermia treatment adequacy (i.e., establishes a method for writing a hyperthermia prescription). In spite of extensive phase II data suggesting that higher temperatures yield improved likelihood for effective therapy, until recently there have been no successful prospective trials showing that escalation of thermal dose yields improved antitumor effect. However, two clinical trials have been reported where thermal dose was controlled during application of hyperthermia.[156,220] These trials set the stage for establishing realistic goals for how to administer this treatment in combination with radiotherapy.

These two trials were designed to perform a "test" hyperthermia treatment first, to determine whether the tumor was heatable, as defined by pre-established criteria. If the tumor was "heatable" then the patient was randomized to receive either a low cumulative thermal dose or a high thermal dose that was at least 10-fold higher than the low dose group. The inclusion of the "test" treatment was key in both studies, as about 12% of all eligible patients were excluded from randomization because their tumors could not be heated. The first trial was in patients with superficial tumors and the second was in pet dogs with spontaneous soft tissue sarcomas. Both trials demonstrated that cumulative thermal doses >10CEM 43°CT_{90} yielded improved tumor responses and durations of local control[156,220] (Figure 21-9). To put this into perspective, this cumulative thermal dose is equivalent to achieving a temperature of 40°C for 1 hour, once or twice a week, at the 10th percentile of the temperature distribution. Importantly, this thermal goal was reached in >90% of patients who randomized to the high thermal dose group.

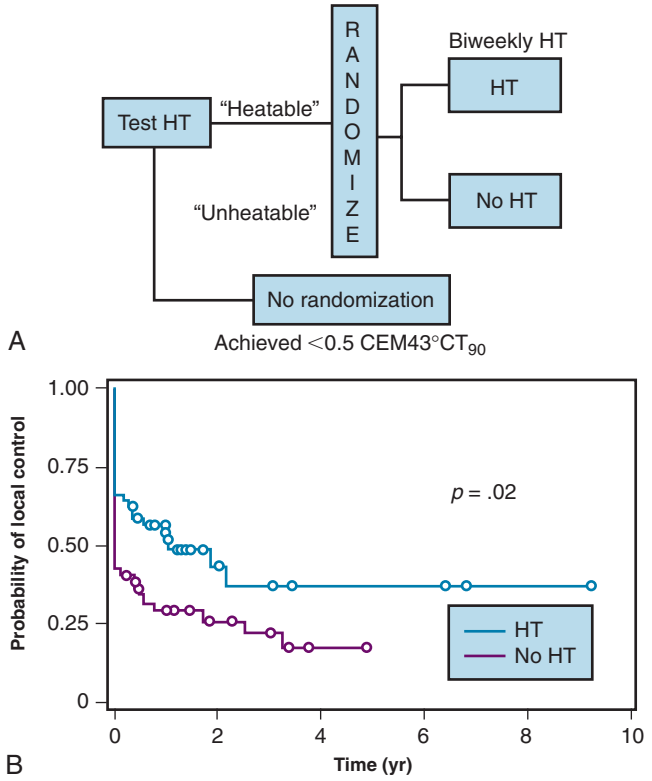

Figure 21-9 **A,** Clinical trial design. **B,** Duration of local control in patients with superficial tumors treated with a low vs. high cumulative thermal dose combined with RT. The difference in CR rate was significant.
Figure reproduced with permission of the author and publisher Jones, 2105.[156]

Future Directions

Tri-Modality Therapies

There are important observations that have been made about hyperthermia that provide strong rationale for its continued development. First, although the addition of chemotherapy to radiation therapy has improved treatment outcome for many diseases, there is still a long way to go. The addition of hyperthermia to chemoradiotherapy protocols may be what is needed to push the therapies further toward the goal of reaching 100% local control. Since hyperthermia provides synergistic interaction with many chemotherapeutics, some targeted drugs as well as radiation therapy, this general approach is compelling.

Augmentation of Drug Delivery

Drug delivery to tumors remains a major challenge due to physiologic barriers such as high interstitial fluid pressure and heterogeneous perfusion. As noted earlier, hyperthermia has been shown to augment macromolecule and nanoparticle drug delivery by increasing blood flow, available volume fraction, and tumor vascular permeability. Furthermore, local hyperthermia can be used as a trigger for temperature-sensitive drug delivery systems such as liposomes, polymers, and hydrogels.[23,28,34,36,241] In this manner, site-specific bioavailability can be achieved. For example, a temperature-sensitive liposome containing doxorubicin (ThermoDox™) has been developed to release rapidly at clinically achievable temperatures of 40°C to 42°C. This formulation has shown dramatic improvement in tumor drug concentration and anti-tumor efficacy in preclinical studies[23,242] and is currently being investigated in phase I/II/III clinical trials for chest wall recurrences of breast cancer and radiofrequency ablation of liver metastases, respectively. As thermal technology and liposomal formulations advance, this method has the potential for precise control of drug delivery independent of tumor phenotype and drug composition.

Newer applications of thermosensitive liposomes have contained both drug and MR contrast agents and this tandem has been used to monitor drug delivery to heated tumors in real time, as the MR contrast agents change the MR signal when released from the liposomes[243-245] (Figure 21-10). There is increasing interest in using the dual MR/drug containing liposomes in combination with high intensity focused ultrasound to enhance drug delivery to a variety of tumor sites, including brain.[23,26,27,145,246-251]

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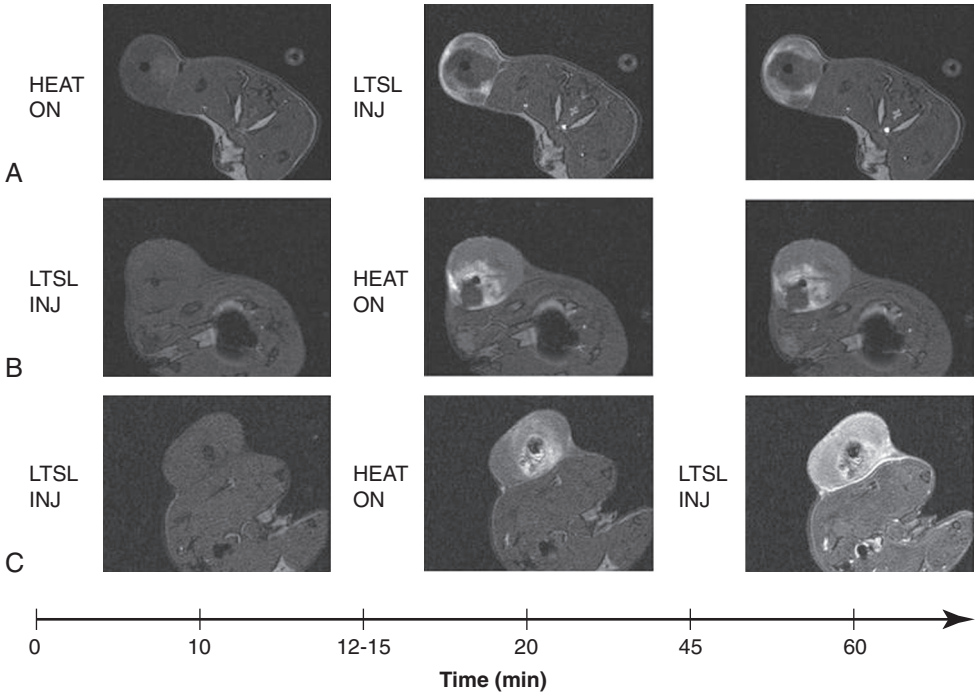

Figure 21-10 Example of monitoring drug delivery in real time, using liposomes containing an MR contrast agent (MnSO4) and doxorubicin. Calibration studies showed that the change in T1 relaxation time, induced by the Mn^{++}, is linearly proportional to drug concentration, in vivo. HT is delivered to the tumor using a catheter containing circulating hot water at the center of the tumor (shows as a dark spot near the center of each tumor). **(A)** When HT is administered, prior to and during drug administration, drug deposition is highest at the periphery of the tumor. **(B)** When drug is administered first, followed by HT, the drug accumulates around the cathether, yielding a centralized drug deposition pattern. **(C)** When drug dosing is split in half and given prior to HT and after HT has started, a more uniform drug deposition pattern is seen. Interestingly, the peripheral drug delivery pattern was most efficacious.[243] *LTSL*, Thermally sensitive liposome.

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A full list of cited references is published online at www.expertconsult.com.

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