Minireview

Thermoradiotherapy in the Management of Superficial Malignant Tumors

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Abstract

In recent years there have been numerous randomized and nonrandomized studies conducted to assess the efficacy of hyperthermia combined with either radiation therapy or chemotherapy, especially in the treatment of superficially seated malignant tumors. The major impact of hyperthermia is currently on locoregional control of tumor. Heat may directly cytotoxic to tumor cells or inhibit repair of both sublethal and potentially lethal damage after radiation. These effects are augmented by the physiological conditions in tumors which lead to states of acidosis and hypoxia. Blood flow is often impaired in tumor relative to normal tissue, and hyperthermia may lead to a further decrease in blood flow and augment heat sensitivity. Three major areas of clinical investigation have borne the greatest fruit for hyperthermia as adjunctive therapy to radiation therapy. These include recurrent and primary breast lesions, melanoma, and head and neck neoplasms. The thermal enhancement ratio was increased in all cases and is estimated to be 1.4 for neck nodes, 1.5 for breast, and 2 for malignant melanoma. In general, the most important prognostic factors for complete response are radiation dose, tumor size, and minimal thermal parameters (minimum thermal dose, mean minimum temperature or temperature exceeded by 90% of thermal sensors). The number of heat fractions administered per week appears to have no bearing on the overall response, which may be indicative of the effects of thermotolerance. The total number of heat fractions delivered also appears to be irrelevant provided adequate heat is delivered in one or two sessions. The major prognostic factors for the duration of local control are tumor histology, concurrent radiation therapy dose, tumor depth, and mean minimum temperature.

Introduction

In the last two decades there has been a great interest in the use of hyperthermia combined with radiation in cancer treatment. This is associated with a greater understanding of several biological parameters such as radiosensitization, chemosensitization, direct cytotoxicity, thermotolerance, and stepdown heating, as well as complex changes in the micromilieu, especially involving the microvasculature. Although hyperthermia as a new and effective modality shows definite promise in the treatment of cancer, the major challenge is the translation of these benefits to clinical practice. This requires cooperative effort and relies on close interaction of biologists, physicists, and oncologists specifically to determine the most important biological parameters affecting hyperthermia, to manufacture devices that can heat deeply and homogeneously, and to determine temperature reliably, consistently, and, ideally, noninvasively. It is obvious that the education of fellow clinicians in the utility of this modality is also very important. This article presents an overview of the clinical application of local microwave hyperthermia for superficial lesions. The practical application of regional and whole-body hyperthermia remains confined to investigational protocols.

The application of heat in the treatment of disease has a long tradition dating to antiquity, but took its modern form only in the last 20 years. Hippocrates is attributed with the statement that "an illness not cured by heat is incurable." The modern era of hyperthermia is thus relatively recent and occurred with the advent of new technology, allowing the use of radiofrequency, microwave, and ultrasound to heat tumors and the advent of nonperturbing thermometry systems.

In 1866 Busch (1) first observed the effect of systemic hyperthermia on possible cancer eradication in human subjects. He reported the disappearance of a sarcoma of the face after a bout of erysipelas. In 1893 Coley (2) reported on 10 patients with advanced malignancies who developed prolonged febrile reactions to erysipelas. Using filtered toxin or mixtures of bacterial toxins (Coley's toxin), he induced pyrogen therapy by injecting the toxins into the tumor itself. In 1909 Schmidt (3) suggested that hyperthermia could be added to radiation therapy as a radiosensitizer.

In the last two decades, there has been a great interest in this modality, culminating in the availability of the first commercial machines. The biological principles underlying the science of hyperthermia are becoming established and many single-institution clinical studies have shown efficacy (4). Criteria of quality assurance are, however, still unresolved and a RTOG study (RTOG 81-04) highlighted the problems in the application of hyperthermia in a multiinstitutional setting (5). These include (a) the difficulties associated with adequate thermometry; (b) the selection of patients with potentially heatable lesions using currently available 915-MHz hyperthermia devices (i.e., ≤3 cm

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The abbreviations used are: RTOG, Radiation Therapy Oncology Group; TER, thermal enhancement ratio; \( d_{min} \), minimum thermal dose; \( T_{mean} \), mean minimum temperature; SAR, specific absorption rate; ESHO, European Society of Hyperthermic Oncology.
Clinical Thermoradiotherapy

Clinical Rationale

Locoregional failure remains a significant cause of cancer death and considerable patient morbidity even when the problem of disseminated metastases is more life-threatening (6). The major impact of hyperthermia is currently on locoregional control of tumor. Heat may be directly cytotoxic to tumor cells or inhibit repair of sublethal and potentially lethal damage after radiation therapy (7, 8). These effects are augmented by the physiological conditions in tumors which lead to states of acidosis and hypoxia (9–11). Blood flow is often impaired in tumor relative to normal tissue, and hyperthermia may lead to a further decrease in blood flow and augment heat sensitivity (12, 13). At lower, more realistic temperatures (≤43°C), blood flow is not affected in human tumors by hyperthermia as it is in rapidly growing experimental tumors (14).

Hyperthermia-induced radiosensitization is a general phenomenon but, in particular, cells in the radioreistant S phase are sensitized to the greatest extent to radiation by heat (15–17). More recently, the interaction of hyperthermia and chemotherapy has gained increasing interest (18). Hyperthermia may increase the cytotoxic effects of certain chemotherapeutic agents, e.g., the alkylating agents, and help to overcome acquired drug resistance (19). Furthermore, it can improve drug delivery to the tumor and possibly modify drug pharmacokinetics (20).

Clinical Experience

Randomized Studies. Despite the fact that more than 11,000 patients had already been treated with hyperthermia by 1984 (4), there have been few prospective, randomized, multi-institutional studies in hyperthermia, and to date a definitive study is still lacking. The RTOG reported on a randomized study (5) of superficial recurrent tumors that were treated with either radiation therapy alone or thermoradiotherapy. The positive feature of this study was that a subset of lesions ≤3 cm in diameter and that had received ≥2 sessions of 42.5°C heat showed an improvement in complete response in the category of breast and extremity lesions. There was also a greater probability of maintaining a persistent response over 12 months (82% versus 12%) in those lesions receiving hyperthermia, indicating a more durable complete response.

A prospective, randomized study was initiated by Valdagni et al. (21) who treated N1 neck disease arising from T1-2 primary lesions or unknown primary sites. Although the number of patients accrued was small, the trial was closed prematurely for ethical reasons. A complete response was noted at 3 months in 82% of patients receiving thermoradiotherapy compared to 37% who were treated with radiation therapy alone (P = 0.01). However, the difference in total response (complete and partial response) was not statistically significant (88% versus 79%). This indicates that many of the patients achieving a partial response with radiation therapy were converted to complete responders by the hyperthermia. A clear distinction between clinical tumor regression and overall tumor control must also be made. Hyperthermia appears to augment tumor control even though initial tumor response may not be significantly improved, which suggests that the clonogenicity of residual viable cells is affected by hyperthermia despite the absence of outright cell death. In a multivariate analysis, Engin et al. (22) showed that radiation therapy dose and tumor volume, but not tumor temperature, were the most significant factors in achieving a complete response (i.e., first one to two decades of cell kill), whereas the duration of local control (total cell kill) was most significantly influenced by tumor temperature and tumor volume rather than by radiation therapy dose.

Earlier work by Arcangeli et al. (23, 24) involved a series of patients with two or more superficial lesions treated with various protocols in separate randomized studies. The best therapeutic effect was obtained by restricting the heat to the tumor site and using large radiation fraction sizes and immediate heat, a schedule designed to produce maximal cytotoxicity. They also observed that tumor control was improved by the use of a larger number of heat fractions and increased thermal dose (t43, minEq42.5°C).

Recently, Valdagni et al. (25) reported on inoperable metastatic lymph nodes in patients with head and neck cancer who were randomized to receive conventionally fractionated radical radiation therapy alone or combined with local hyperthermia. The addition of hyperthermia significantly improved early response rate and 5-year actuarial nodal control in the absence of severe toxicity.

Preliminary results of two major European multiinstitutional studies appear to be very promising (26, 27). In ESHO protocol 3-85, 134 metastatic or recurrent malignant melanoma lesions were randomized to receive radiotherapy alone (3 fractions in 8 days; 3 × 8 Gy or 3 × 9 Gy) or each fraction followed by hyperthermia. Two-year actuarial local tumor control was 28% in the radiation-alone group and 46% in the thermoradiotherapy group (P = 0.008). Cox multivariate regression analysis showed that the most important prognostic parameters were hyperthermia (P = 0.02), tumor size (P = 0.05), and radiation dose (P = 0.05). Addition of hyperthermia did not significantly increase the acute or late radiation reactions. In a collaborative phase III superficial hyperthermia trial in primary and recurrent breast cancer lesions conducted by several institutions (Medical Research Council, ESHO, Princess Margaret Hospital), it was indicated that complete response rate could be increased from 40% (radiation alone) to 60% with the addition of hyperthermia (27). The difference was statistically significant.

Nonrandomized Studies. In numerous, nonrandomized single-institution studies, the benefit of hyperthermia has been clearly demonstrated and is remarkably consistent in showing an advantage in favor of hyperthermia for all histologies in all sites tested (28). A therapeutic gain is suggested in spite of the wide diversity of techniques used for heating, thermometry, and criteria for assessment of response. The thermal enhancement ratio ranged between 1.2 and 5.4. Several studies of matched and paired lesion analysis in the same patient similarly confirmed the therapeutic benefit of hyperthermia (29, 30).

The difficulty of uniformly heating apparently favorable, superficial sites in areas where problems of contour and shape are minimal has been well described. Dunlop et al. (31) reported that 58% of the patients treated with thermoradiotherapy reached a minimum thermal dose of 20 minEq43°C and 24% reached 60 minEq43°C and could achieve 20 minEq43°C at each

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occasion. However, 23% of tumors could not be heated effectively at any time. The tumors that were effectively heated had a complete response rate of 86% versus 35% for those inadequately heated (P < 0.001). The complete response rate of lesions receiving radiation therapy alone was also 35%. This study emphasizes the need to achieve a thermal distribution to minimum threshold temperatures.

Additional difficulties in heating capability arise from the site being treated. The head and neck region is more difficult to heat because of several factors, including changing contour and poor applicator apposition, the extent and depth of tumor, and the tolerance of the patient.

**Prognostic Factors.** Three major areas of clinical investigation have borne the greatest fruit to demonstrate the benefit of hyperthermia as adjunctive therapy to radiation therapy. These include recurrent and primary breast lesions, malignant melanoma, and head and neck neoplasms. The TER was increased in all cases and is approximately 1.4 for neck nodes, 1.5 for breast, and 2 for malignant melanoma. Because of the apparent lack of histological specificity to thermosensitivity, sarcomas and other traditionally radioresistant tumors are also eminently suitable for this modality, provided they are accessible and of a size that is potentially heatable using currently available 915-MHz hyperthermia devices, i.e., ≤3 cm depth (32). In general, the most important prognostic factors for complete response are radiation therapy dose, tumor size, and minimal thermal parameters (Tmin, Tmin, or temperature exceeded by 90% of thermal sensors). The number of hyperthermia fractions administered per week appears to have little bearing on the overall response, which may be indicative of the effects of thermotolerance (22, 33, 34). The total number of heat fractions delivered also appears to be irrelevant, provided adequate heat is delivered in one or two sessions (33). The administration of multiple fractions of heat is advantageous only in leading to a greater probability of achieving at least one good heat session and allowing full coverage of the tumor if a multiple field “patchwork” approach is adopted (35). The major prognostic factors for the duration of local control were tumor histology, concurrent radiation therapy dose, tumor depth, and Tmin (22, 33, 36–38).

**Criteria for Suitability for Superficial Localized Heating.** The selection of the sites and types of lesions that are appropriate for this approach have been described by Kapp (39). The most important indication for hyperthermia is the determination that a poor response is likely if radiation therapy alone was to be applied. This would apply to radioresistant histologies, recurrent disease, or excessive bulk of tumor. The combination of hyperthermia and radiation therapy is an attempt to improve the therapeutic ratio and is akin to surgery and radiation therapy in being a form of localized combined modality treatment. The most important criterion is accessibility both in size and depth of lesion. Flat surfaces such as the chest wall and the limbs are ideally suited for external applicator heat. The depth of the lesion is critical and for practical purposes is limited for microwave applicators to a maximum of 3–4 cm with 915-MHz microwave and 7–8 cm if 1-MHz ultrasound is used (40–42). The presence of bone and air-tissue interfaces in the treatment volume precludes the use of ultrasound. Cystic lesions may be heated to a greater depth because of decreased blood flow. In general, patients should have a reasonable performance rating, sufficient to withstand a 60-min session of heat therapy, and should have a life expectancy of ≥2 months for tumor response to be monitored.

**Carcinoma of Breast.** Locoregional failure in the breast still constitutes an important cause of morbidity and suffering, even when overshadowed by the problem of distant metastases. Even after radical or modified mastectomy, the local recurrence rate is 10–40% depending on size, tumor characteristics of the primary, underlying fixation, the presence of grave signs, and the number of regional lymph nodes involved (43).

There are few randomized studies of hyperthermia in chest wall disease. At least 40% of the patients evaluated in the RTOG study 81-04 had carcinoma of the breast (5). Although the overall result for all patients showed no significant difference between the two arms (30 and 32%, respectively), 62% of the patients with lesions ≤3 cm had a complete response versus 40% with radiation therapy alone. Besides size, radiation therapy dose was also critical. van der Zee et al. (44) treated patients with recurrent carcinoma of the breast in combination with hyperthermia. Based on this experience, the authors suggested that a total dose of 32 Gy in 8 fractions administered with twice-weekly fractionation and accompanied by hyperthermia is safe and efficacious. Engin et al. (35) reported excellent palliative results by using patchwork hyperthermia fields in extensive chest wall recurrences due to advanced carcinoma of breast.

Although most studies have concentrated on locoregionally recurrent lesions, advanced primary breast carcinoma is also an appropriate situation for evaluating the role of hyperthermia, especially when the presence of grave adverse prognostic features makes local control distinctly remote. Results with radiation therapy alone are poor, with 45–65% of tumors recurring locally (45). Vora et al. (46) treated patients with inoperable and inflammatory carcinoma of the breast with a combination of external and interstitial radiation therapy and interstitial hyperthermia. With follow-up of 11–36 months, local control was obtained in 80% of patients. Similarly, Puthawala et al. (47) reported 88% local control with radiotherapy using combined external and interstitial radiation therapy to total doses of 80–90 Gy and accompanied by interstitial hyperthermia.

The role of hyperthermia in an adjuvant setting where there is no gross evidence of residual disease is undefined. Because of the presence of large amounts of normal tissue and minimal tumor elements, there would seem to be questionable indication for hyperthermia. However, this must be viewed in context, and factors such as patients’ age and general condition must be considered as well as the risk of recurrence with conventional radiation therapy. Kapp et al. (48) recently reported a positive experience with thermoradiotherapy for residual microscopic cancer. Various attempts to address the problem of tumor thickness and extent on heatability have included the use of multiple applicators, overlapping patchwork hyperthermia (35), combined interstitial and external applicator techniques to heat more deeply and uniformly (49), and the use of multiple separately powered heating elements, which can be tailored to encompass wide surface areas (50).

**Malignant Melanoma.** Local control is an important determinant of length of survival in this disease even though distant metastases is the major cause of death. Overgaard (51)
showed that local control was improved by locoregional hyperthermia. He also found that the radiation therapy fraction size was an important prognostic factor. Emami et al. (52) reported on superficial recurrent, primary and metastatic malignant melanoma lesions. They found that a thermal dose of 200 min_{43°C} was associated with a 100% complete response. Engin et al. (53) observed a similar correlation between complete response and the minimum thermal dose during the first heat session. In a large study, Overgaard and Overgaard (54) reported an improvement in locoregional control in patients receiving hyperthermia. The radiation therapy dose required for 50% control was reduced by hyperthermia with a TER of 1.43 for simultaneous treatment and 1.24 for sequential treatment, i.e., radiation therapy followed 4 h later by heat. Tumor control was also more durable with hyperthermia. The rate of persistent local control at 18 months was increased by the hyperthermia (86% versus 56%, P < 0.05). Although a high TER was obtained with simultaneous treatment, normal skin tissue reaction was also increased, thus yielding no improvement in therapeutic ratio. With sequential treatment, i.e., heat given at least 4 h after radiation therapy, normal tissue sensitization did not occur, resulting in a therapeutic gain of 1.22.

The favorable impact on larger tumors was reported earlier by Kim et al. (55), which was attributed to greater heatability of tumors to minimum tumor temperatures of 42°C. Radiation dose per fraction was demonstrated to be critically important in tumor control. Smaller tumors treated with high doses per fraction showed no beneficial effect of hyperthermia. With larger tumors, hyperthermia increased the rate of response and accelerated tumor regression with both large and small radiation therapy doses per fraction. Hyperthermia appeared to aid in overcoming the adverse effects of large volume disease and the use of low radiation therapy fraction sizes. It was associated with a TER of 1.5.

**Head and Neck Tumors.** Despite the aggressive use of combined modality therapy in the head and neck region, locoregional disease is the most important mode of failure. Hyperthermia has been applied to the head and neck region mainly for nodal and metastatic deposits. In most cases, because of depth of the tumor, the primary site cannot be adequately heated with currently available external microwave equipment, and an interstitial implant is required for hyperthermia to be effective. This region presents considerable technical challenge because of rapidly changing contours and difficulties with coupling the external applicator to the tumor. Lesions are frequently extremely large and irregular in shape and cannot be well encompassed by available external applicators. Often tumor is endophytic, extending deeply to the parapharyngeal space and base of skull region or situated deeply beneath muscle and other normal tissue.

**Primary Treatment.** Arcangeli et al. (23, 56) have reported on the use of multiple daily radiation therapy fractions and hyperthermia on N₂-N₃ multiple cervical lymph nodes. Matched lymph nodes were used in the same patient. A higher complete response rate was obtained for the combined treatment compared to hyperfractionation alone or to a historical series of conventionally fractionated radiotherapy. A TER of 1.9 was obtained. When thermal dose was above 200 min_{42.5°C}, all responses were complete irrespective of volume. The combined use of hyperfractionation and hyperthermia in primary disease of the head and neck in a nonrandomized trial setting also makes this experience distinct. In a prospective randomized study with N₃ disease arising from T₁-T₂ lesions or unknown primaries, Valdagni et al. (21, 25) reported that the results were highly significant in favor of thermoradiotherapy.

**Recurrent Tumor.** It is clear that complete responses in the order of 50–85% may be obtained in advanced nodal disease in the head and neck with the combination of high-dose radiation therapy and hyperthermia. The effectiveness of standard radiation therapy may thus be improved without increased serious morbidity. This approach may help certain patients with advanced tumor to overcome the prognostic implications of inoperability by producing sufficient tumor shrinkage to allow resection to be performed. The major constraint is the ability to heat tumor adequately. Thus major limitation at this time is largely technical and relates to the difficulty in delivering heat sufficiently deeply to the whole tumor. In attempts to treat large nodal masses that are recurrent after full conventional therapy, a combination of interstitial and external applicator heat has been applied (49). This approach allows catheters to be inserted into the base of the lesion for continued use of interstitial heating and interstitial radiation therapy and thermometry. Treatment of such masses presents considerable technical difficulties due to the greater medial extension than is appreciated clinically. For this reason, computed tomographic scanning is crucial in planning the placement of the temperature catheters (57). Interstitial hyperthermia in combination with external beam and interstitial radiation therapy has also been applied to advanced and locally recurrent primary disease (58).

**Skin Reactions.** Several randomized and nonrandomized studies comparing radiotherapy alone with the combination of radiation and hyperthermia have shown that skin reactions were not increased significantly by the addition of hyperthermia. Gonzalez Gonzalez et al. (59) observed enhancement of acute skin reactions, although the enhancement did not constitute a clinical problem (59). Lindholm et al. (30) reported that local pain and normal tissue reactions were a problem with 2450-MHz microwaves but were reduced when 915-MHz microwaves were used. Gabriele et al. (60) treated 60 lesions with hyperthermia alone. They observed skin burns in two cases (3%). Other side effects were blisters with moist desquamation (10%) and local infection after invasive procedures of thermometry (13%).

In their randomized study of the effects of thermoradiotherapy on spontaneous tumors in pets, Dewhirst and Sim (61) found that the incidence of direct thermal injury to skin was positively correlated with maximum intratumor equivalent minutes at 43°C. They also concluded that little or no enhancement of early or late radiation effects occurred with the addition of hyperthermia. In studies on human tumors, Luk et al. (62) showed a positive correlation between the incidence of burns and blisters and the intratumoral temperature maxima. Howard et al. (64) showed that the average maximum skin heat dose per treatment correlated with the incidence of severe skin reactions, and Seegenschmiedt et al. (64) showed a correlation between total mean and maximum tumor thermal dose and acute complications. Kapp et al. (65) showed that the average of the maximum tumor temperature and the number of hyperthermia
treatments per field were the most important predictive factors for complications in thermoradiotherapy. Engin et al. (66) showed that the presence or absence of previous radiation therapy, previous radiation therapy dose, concurrent radiation treatment factors, i.e., concurrent radiation dose, number of elapsed days, the minimum tumor temperature factors of $T_{\text{min}}$ and $T_{\text{3min}}$, and the number of hyperthermia treatments all correlated with occurrence of skin reactions.

**Hyperthermia Trials.** Despite a strong scientific basis for hyperthermia, its true efficacy when given as an adjuvant to primary radiotherapy still needs to be fully evaluated in an objective randomized multinstitutional study. In this context, the early and late tolerance of normal tissues also requires assessment. The identification of the technical, biological and clinical variables affecting tumor response and normal tissue tolerance remains the critical issue that will eventually lead to standardization of thermometry, method of heating, fractionation schedules, and quality assurance. Various international societies have been actively involved in conducting clinical trials to achieve these objectives. In investigating the role of hyperthermia in primary treatment, a strong priority is to minimize the risk of severe late complications. With this in mind, the general principle is to recommend conventional fractionation and to supplement this with hyperthermia either once or twice weekly.

The combination of external applicator heat and chemotherapy, especially cis-platinum for the treatment of refractory superficial malignancies is also under investigation (67). This is designed for patients who have already received full dosage radiation therapy often in multiple courses of treatment. The use of all three modalities delivered concurrently (trimodality therapy) is also being investigated in single-institution studies (19). This form of therapy holds considerable promise because of the synergistic interaction of any two of the three modalities and has been found to be efficacious in vitro (68). cis-Platinum in combination with radiation therapy is being closely investigated in several radiotherapy studies and seems to produce less sensitization of normal tissues compared to other agents. Maximum cytotoxicity occurs when these modalities are administered simultaneously, but optimal dose scheduling and sequencing of therapy needs to be investigated in clinical studies.

**Quality Assurance.** The need for quality assurance in hyperthermia is particularly great at this time because of the lack of standardization of equipment and techniques used for heating and monitoring temperatures. There are few objective criteria with which to judge the quality of heat treatment and quantitative assessment of patients derived from different institutions is fouled by variability in patient treatment and temperature data (40-42). Of particular importance is ensuring the adequacy of heating patterns for a given tumor volume while limiting normal tissue heating. Since there is no direct relationship between the SAR pattern derived from phantom studies and temperatures achieved in perfused tissue, considerable experience is required to choose the appropriate applicator for a given tumor size and site. In general, the tumor volume and margin should be encompassed by the 50% isoSAR (i.e., 50% surface SAR) and placement arranged to maximize power coupling and minimize reflected and stray electromagnetic leakage. Unfortunately, this often requires the use of an applicator roughly twice the surface area of the lesion, which may not always be feasible depending on the location of the tumor. Moreover, the SAR pattern rapidly constricts with depth and a lesion of appreciable thickness may not be adequately heated even with a generous applicator (69–72).

An area of particular concern is the standardization of thermometer placement within the tumor. The need for ample multipoint thermometry or thermal mapping cannot be overemphasized. The RTOG Thermometry Task Force has formulated recommendations and guidelines for the insertion of catheters for monitoring tumor temperature for both microwave (70) and ultrasound (72) modalities. Verification of thermometry catheter placement with computed tomographic scans is necessary in tumors of $>1.5$ cm depth, both to confirm that the catheters in fact traverse tumor and to determine the depth of placement (57). Documentation of catheter locations relative to tumor margins is mandatory. Thermal mapping should be employed by using multisensor thermal probes, preferably performed mechanically under computer guidance.

**Areas of Future Development.** The major limitation at this time is the inadequacy of current equipment to deliver power homogeneously to tissue and allow inclusion of tumor volumes of greater extent and depth. No less important is the availability of temperature monitoring systems that will accurately reflect the tumor temperature with good resolution and without significant artifact. A severe drawback at this time is the necessity to resort to invasive thermometry and the need to insert multiple multiarray temperature sensors in order to assess tumor temperature adequately. Improvement in protocol design and analysis, taking into account all important prognostic factors and stratifying for them, also needs to be achieved. The combination of whole-body hyperthermia in addition to locoregional heat is being investigated both as a means of producing greater homogeneity in the heating pattern and raising the minimum tumor temperature to therapeutic levels (73). The interaction of chemotherapy and hyperthermia is also being explored in early phase I/II studies separately and in combination with radiation therapy and has enormous potential for clinical use.

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