HYPERTHERMIA IN CANCER THERAPY: WHERE ARE WE TODAY AND WHERE ARE WE GOING?

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ALTHOUGH CLINICAL hyperthermia was used decades ago with impressive anecdotal reporting,[1] much of the enthusiasm 10 years ago for trying hyperthermia in cancer therapy was based on information emanating from the laboratory.[2] Some transplantable tumors in mice were destroyed by time-temperature combinations that did not permanently damage normal tissue.[3] Additional information from the laboratory is summarized below.

Two distinct effects of heat may contribute to the control of cancer: first, heat kills cells directly, and second, heat sensitizes cells to ionizing radiation or drugs. Both effects of heat may be observed at temperatures between 40.5°C and 45°C, but direct cell killing is usually weak below 43°C. Some neoplasms seem inherently more sensitive to heat than the normal cells from which they arise, but this is not true of all neoplasms.[4]

It is generally recognized that hyperthermia has greater potential benefit in cancer therapy when coupled with another treatment modality such as ionizing radiation. Mechanisms by which heat may sensitive cells to ionizing radiation are: reduced ability of heated neoplastic cells to repair sublethal and potentially lethal damage;[5] increased thermal sensitivity of hypoxic-acidotic tumor cells;[6] complementary cell sensitivity to heat and radiation during different phases of the cell cycle.[7]

WHERE ARE WE TODAY?

At the present time clinical hyperthermia is often used with limited doses of ionizing radiation to palliate recurrences of previously irradiated tumors. However, as more patients are referred with smaller unirradiated tumors, they are receiving hyperthermia combined with larger doses of radiation. For example, by combining hyperthermia with slightly less than "curative" doses

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of radiation, we may achieve the expected local control rate with fewer therapeutic complications. Alternatively, hyperthermia combined with the highest tolerated doses of radiation may increase local control beyond levels achievable with radiation alone.[8]

Because hyperthermia is not mutagenic, not myelosuppressive, not compromised by previous therapy, and is synergistic with radiation and certain drugs, an initial wave of enthusiasm favored hyperthermia in cancer therapy.[9] However, this initial enthusiasm has been gradually tempered as we begin to understand that several problems persist in the delivery of clinical hyperthermia today. One is our partial understanding of how best to combine hyperthermia with other cancer therapy modalities. Since the number of patients referred for hyperthermia is relatively small, better animal model systems need to be developed and utilized.[10] The second problem is our inability to deliver uniform heating to deep tumor sites in the thorax and upper abdomen.[11] Less toxic forms of whole body hyperthermia may need to be tried for tumors in these areas. Third is the difficulty in heating tumors selectively. Hyperthermia applied to large volumes of normal tissue will limit patient tolerance and may contribute to late complications.[11] Finally, our ability to monitor the temperatures throughout the heated volume is impaired by the requirement for invasive thermometry. Though eased by the development of thermal mapping,[12] multisensor probes,[13] and thermal modelling,[14] this problem will only be solved when a reliable noninvasive form of thermometry has been discovered.

Whole body hyperthermia. Since whole body hyperthermia addresses cancer as a systematic disease, its proponents argue that it has the greatest potential for curative success when used as an adjunct to other therapeutic modalities.[15] However, its detractors argue that in the past this modality has caused significant morbidity and occasional mortality. Most systems for whole body hyperthermia require general anesthesia with endotracheal intubation and complex equipment to regulate patient temperatures. The system most used to date worldwide has been direct extracorporeal blood-warming. This requires the surgical placement of vascular shunts.[16] It has been feasible to use extracorporeal heating in combination with both radiation and chemotherapy. A hot water suit system, developed at the National Cancer Institute, has also undergone extensive clinical trials.[17]

Recently a team at the University of Wisconsin developed a radiant heat system for whole body hyperthermia. The advantages of this system are that it does not require general anesthesia with endotracheal intubation; it allows for multiple treatments per week; and it lends itself to a multimodality

approach. Following a phase I clinical trial with whole body hyperthermia alone, several second generation studies have been reported. These include its combination with interferon[18] with local radiotherapy for non-small cell lung cancer,[19] with lonidamine,[20] with carboplatin,[21] with low dose total body radiation for favorable B cell lymphomas,[22] and in a setting of allogeneic bone marrow transplantation.[23] As of 1990 more than 650 treatments have been performed by this group without significant clinical toxicity. It appears that the stage has been set to design and perform a prospective, randomized phase III trial to evaluate the efficacy of whole body hyperthermia.

Local hyperthermia. Local hyperthermia is generally used to heat superficial tumors to temperatures of 42 to 45°C with minimal damage to normal tissues. Different technologies have been developed that externally deposit heat to treatment areas. These include capacitive, electromagnetic, and ultrasound heating.

Capacitive heating involves placing part of the body within an electrical circuit. The patient circuit is tuned to resonate with the generator frequency (usually 13.56 and 27.12 MHz). However, such inhomogeneities as fat or muscle interfaces parallel to the capacitive plates cause preferential heating of fatty tissues.[24] Tumors may also be heated by inducing eddy currents electrically in tissues by alternating magnetic fields. Here again, the distribution of heat intensity depends on the electric and magnetic field strength, often most intense near the body surface. The best-known commercially available system to utilize induction heating is called a Magnetrode.[25]

During the past decade microwaves have become a popular way to induce local hyperthermia. When biological tissues are exposed to microwave irradiation, electric and magnetic fields are induced within the tissues. These fields give rise to ionic currents and molecular excitations that heat adjacent tissue cells.[26] For hyperthermia applications frequencies of 434, 915, and 2450 MHz have been studied extensively. The last frequency has the least penetration and moreover produces pronounced hot spots at the fat and muscle interfaces. Lower frequencies provide better penetration and fewer inhomogeneities of power absorption.[27]

Ultrasound also propagates in tissue and its energy loss leads to tissue heating. It is commonly used in the frequency range of 0.3 to 5 MHz. Its short wavelength on the order of millimeters allows deeper penetration into soft tissue than hyperthermia from electromagnetic waves.[28] Ultrasound has been focused to depths of about 10 cm in homogeneous tissue-equivalent materials; however, there is significant reflection by air cavities and bony surfaces.[29] Bones in the path of an ultrasonic beam can act as high absorbers

COMPARISON OF TUMOR RESPONSE RATES AFTER IRRADIATION ALONE VS. IRRADIATION COMBINED WITH LOCAL HYPERTHERMIA

Clinical trial	*Complete response rate (%)*	
	Irradiation alone	*Irradiation plus hyperthermia*
Recurrent breast cancer		
Palliative radiation doses (16–45 Gy)		
Dunlop et al.[32]	50	60
Lindholm et al.[33]	25	57
Overgaard et al.[34]	40	78
Steeves et al.[35]	31	65
Higher radiation doses (48–66 Gy)		
Perez et al.[38]	51	86
Scott et al.[37]	47	94
Cervical nodal metastases from head and neck cancers		
Arcangeli et al.[38]	42	79
Scott et al.[37]	22	88
Valdagni et al.[39]	37	82
Metastatic melanoma		
Arcangeli et al.[40]	53	76
Emami et al.[41]	24	59
Kim et al.[42]	46	75
Overgaard et al.[43]	57	90

and lead to hot spots. These characteristics of absorption and reflection can bring about significant nonuniformity of heating. Investigators at Stanford University[30] and at the Massachusetts Institute of Technology[31] have developed sophisticated systems utilizing computer-steered and focused transducers that limit the heating of normal tissues and maximize the heating of tumor tissues.

Local hyperthermia has been applied clinically in the treatment of recurrent breast cancer involving the chest wall, lymphadenopathy related to head and neck cancer, and superficial, metastatic, or recurrent malignant melanoma. Other tumor types studied to a smaller degree include lymphomas, sarcomas, and gynecological malignancies metastatic to superficial lymph nodes. Many trials of local hyperthermia and radiation therapy for superficial metastatic nodules have been reported; most of these studies have only historical controls for radiation therapy alone. Hyperthermia and radiation therapy schedules have varied, and temperature distributions produced in tumors were generally not well characterized. Nevertheless, some studies include matched-pair analyses (i.e., comparisons with unheated but irradiated control lesions) as summarized in the table, and these studies consistently showed an advantage for combined modality therapy compared with radiation therapy alone (about 76% vs. 40%).

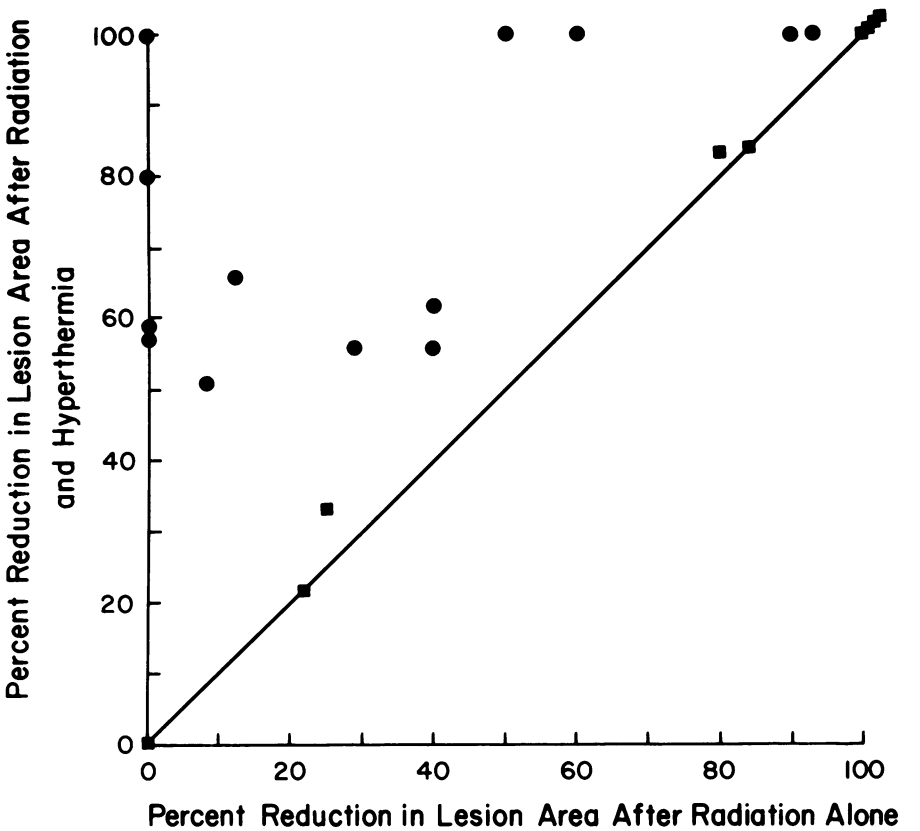

Fig. 1. Matched pair analysis of response to therapy for lesion pairs within the same patient. ● = lesion pairs in which heated areas responded better than unheated areas. ■ = lesion pairs in which there was no difference. Reproduced by permission from Steeves, R.A., Swerson, S.B., Paliwal, B.R., et al.: Matched pair analysis of response to local hyperthermia and megavoltage electron therapy for superficial human tumors. *Endocurie Hyperthermia Oncol. 2:*163–70, 1986.

At the University of Wisconsin we compared the percentage of reduction in lesion area among 22 randomly matched pairs of lesions in 20 patients with multiple superficial neoplasms.[35] The "experimental" lesions were treated by radiation and local hyperthermia (43°C for 1 hour), while the "control" lesions were given the same dose of radiation only. As shown in the figure, about two thirds of the heated lesions responded better than their unheated controls, whether they were evaluated individually by area or regionally by completeness of response.

Considering the results cited above, we were disappointed to see the preliminary results of a randomized study from the Radiation Therapy Oncology Group (Protocol RTOG 81-04). The overall complete response rate in patients treated with irradiation and hyperthermia was only 32%, no higher

than the 28% complete response rate observed in patients treated by radiation alone.[44] However, patients were stratified according to the size of their lesions, and closer inspection revealed that only 22% of the tumors in this study were smaller than 3 cm in diameter and therefore likely to be heated adequately by the external microwave equipment predominantly used. It was encouraging to note that 80% of these smaller lesions treated by both modalities remained in response 12 months later, in contrast to 15% of those treated by radiation alone. However, for the lesions larger than 3 cm the probability of remaining in response was similar in both treatment arms. Retrospective study revealed significant difficulties in achieving "good heating" (i.e., an average tumor temperature greater than 42.5°C for 45 minutes) for 65% of tumors larger than 3 cm in diameter.

Lack of a clearly established quality assurance methodology undoubtedly weakened the ability of Protocol 81-04 to confirm reports of the efficacy of hyperthermia and radiation for lesions larger than 3 cm in diameter. Therefore, a new protocol is being initiated that will employ a wider variety of hyperthermia applicators that can be consistently matched to lesion size and depths, and that will apply strict quality assurance guidelines for all aspects of treatment delivery and documentation.

Regional and interstitial hyperthermia. Beyond the technological difficulties inherent in local hyperthermia and thermometry there is a biological limitation to effective hyperthermia for all cancer cells. Cancer refractory to conventional therapy tends to be more extensive than revealed by current technology, often involving deep body tissues. Thus, local hyperthermia by its very nature is often limited to a palliative role.

One approach to heating deep-seated tumors has been to apply various technologies used for external local hyperthermia at regional levels. That is, microwave or electromagnetic induction applicators or coils placed circumferentially around the body have been used in an attempt to heat entire regions of the body. In general, this has not been successful for thoracic and upper abdominal heating, but there has been limited success with tumors in the pelvis.[11]

Another approach takes advantage of the interstitial technology already developed to irradiate tumors by brachytherapy so that deep tumors can be heated as well as irradiated from within. This utilizes the same catheters used for the afterloading irradiation technique, but of a size sufficient to allow insertion of a microwave antenna along the length of the catheter.[45] Potential advantages of this technique include improved homogeneity of heating and the ease of temperature probe placement via the catheters.[46,47]

Where Are We Going?

The use of whole body hyperthermia may ultimately have its greatest importance in combination with adjuvant chemotherapy. In an earlier review[15] Robins argued that the goal would be to sterilize micrometastases in patients with a high risk of recurrence after primary surgical treatments for such advanced localized cancers as stage C colorectal cancer, stage 2 breast carcinoma, and stages 1 and 2 malignant melanoma. To elaborate on the second example, one third of stage 2 breast cancer patients relapse within five years in spite of adjuvant chemotherapy. It was initially thought that these relapses resulted from drug resistance, but these same patients respond again to the same drugs given in the adjuvant setting. If some of these recurrences resulted from inadequate microvasculature, which thereby caused a failure of drug penetration at a critical time in tumor growth, it could be argued that hyperthermia, and especially whole body hyperthermia, may be of value in an adjuvant setting by increasing drug sensitivity, perhaps by increasing membrane permeability or by altering cellular metabolism.[15] The organization required to conduct a phase III, multi-institutional, clinical trial of adjuvant whole body hyperthermia and chemotherapy is feasible but difficult, and has not yet been initiated.

In the field of local hyperthermia several clinical studies support the concept that the lowest temperature achieved in a tumor mass is the most significant prognosticator of response to the hyperthermia.[48] This concept is being refined further through more sophisticated thermal mapping to evaluate the prognostic significance of temperatures maintained throughout 50% to 90% of the tumor volume.[49] One of the most important areas of current research in local hyperthermia is the development of reliable noninvasive thermometry. NIH investigators[50] have adapted a 0.5 tesla whole-body magnetic resonance imaging (MRI) system to a modified mini-annular phased array designed for heating human limb tumors. The latter was modified to be compatible with MRI by removing all of the original ferromagnetic parts and rewiring it. Temperature images were obtained noninvasively with 0.5°C accuracy, using two 3.5-minute scans of a phantom made of doped acrylamide gel. The spatial resolution for this temperature accuracy was better than 1 cm. Construction is now progressing on a unit that will allow simultaneous heating and imaging.

An exciting new approach to interstitial hyperthermia involves the use of ferromagnetic thermoseeds. In this approach thermoseeds[51] or specially constructed wires,[52] typically 1 mm in diameter and 1 to 7 cm in length, are placed in the interstitial tubing used for brachytherapy. Usually just before

and just after insertion of the radioactive sources, an externally applied electromagnetic induction field is used to heat the thermoseeds in a contactless manner. That is, thermoseeds placed in an oscillating magnetic field become self-contained heaters for which no cable connections are required. These seeds are usually made from special alloys that lose their ferromagnetic properties at a specific temperature, called the Curie point, and this leads to automatic temperature regulation.[53] This new approach has been studied preclinically for several years, and is now being introduced into phase III clinical trials.

Future approaches may involve integration of ferromagnetic hyperthermia with brachytherapy approaches such as the use of a low energy radioisotope like iodine-125.[54] Experiments are currently in progress on the treatment of transplanted choroidal melanomas in rabbits to determine if radiation and hyperthermia are best combined simultaneously or sequentially.

In summary, the use of hyperthermia in cancer therapy has passed through periods of initial optimism and subsequent reassessment, and is now entering a time of qualified acceptance as technological improvements continue.

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