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Hyperthermia
F. K. Storm, MD*

This report describes the history of hyperthermia and reviews current forms of treatment at both low (42°-43°C) and higher (<45°C) temperatures. Hyperthermia treatment at low temperatures includes fluid immersion and irrigation, regional perfusion with heated fluids, and electromagnetic radiofrequency waves. Low-temperature hyperthermia has also been combined with radiation therapy and with chemotherapy in recent clinical trials. At higher temperatures, we and other investigators have also had promising, preliminary results in treating tumors safely. With the specialized radiofrequency instrumentation we have developed to apply hyperthermia at any depth without preferential surface tissue heating, further clinical investigation of both superficial and deep internal solid tumors is now possible.

Recent data suggest that hyperthermia may be an especially effective form of therapy for larger tumors that resist standard forms of treatment. Clinical trials are now underway to determine the most therapeutic dose/time regimen, to determine toxicity and therapeutic enhancement ratios of combined chemotherapy and x-irradiation with hyperthermia, and to evaluate any changes in the host immune system with such therapies.

The use of heat in cancer treatment dates back to the ancients with the application of red-hot irons by Ramajama (2000 BC), Hippocrates (400 BC), and Galen (200 AD). In more recent times, Westermark (1898) placed hot-water circulating cisterns into advanced carcinomas of the uterus and found palliative shedding of some tumors. Coley (1927) introduced “toxin” therapy for cancer, but stated that responses were associated with temperatures of 39°-40°C of several days’ duration, suggesting that the febrile reaction might have been caused by the tumoricidal agent. Simultaneously, Keating-Hart and Doyen (1910) introduced electrocoagulation of tumors, which is still in use today. Warren (1933) was one of the first to apply heat from infrared and high-frequency currents to tumors and found remissions of some cancers. With the subsequent development and popularity of x-irradiation therapy, hyperthermia research was all but abandoned until modern times when the selective thermosensitivity of tumor cells was more fully appreciated.

At temperatures between 41°-45°C (106°-113°F), cancer cells are slightly more sensitive to heat than their normal cell counterparts. In vitro and in vivo tumor models have shown irreversible damage and complete regression of various tumors at 42°-45°C, while normal cells were killed at temperatures at least one degree higher, or more than twice the duration of heating (1-4).

Heat causes progressive necrosis to tumor cells at these temperatures but not in stromal or vascular cells within tumors, nor in normal surrounding tissues (5). Autolytic disintegration of heat-damaged cells is followed by a marked increase in connective tissue stroma and scar formation (6). Interestingly, this process occurs in tissue cultures of tumor-derived and tumor-producing cells, but not in normal and non-tumor-producing cells. When a cell subline derived from a non-tumor-producing line acquires high tumor-producing capacity, it also acquires greater thermosensitivity. Thus, malignant potential, both in vivo and in vitro, is accompanied by decreased thermotolerance (7-8).

Hyperthermia alters both DNA and RNA synthesis and depresses cellular enzymatic systems required for cell metabolism and division. Its major mode of action may be to increase cell and lysosome membrane permeability, caus-

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ing selective internal destruction of the cancer cell. Cells that are less well oxygenated seem to be most vulnerable to thermic injury.

Modern Concepts of Low-Temperature Hyperthermia

Hyperthermia has been applied by various means, including fluid immersion and irrigation, regional perfusion with heated fluids, and by electromagnetic radiofrequency waves.

All frequencies of radiofrequency waves appear to heat tissues in a similar way. Energy is transferred into tissue by field interaction that causes ions in the tissue to oscillate or produces changes in the magnetic orientation of molecules, which are locally converted into heat. Because the energy of a shortwave or microwave quantum is only about $10^{-19}$ eV, it cannot produce ionization or excitation. The biological effects of radiofrequency waves are primarily and perhaps solely due to heat production. However, the absorption and penetration characteristics of electromagnetic waves are markedly dependent upon tissue composition and interfaces (i.e., skin/muscle/fat/bone). Moreover, the depth of penetration is often limited. Incident energy absorption is a function of tissue resistance, so that tissues with high values (skin, subcutaneous tissue, bone) preferentially absorb heat in amounts 10-150 times greater than tissue with low values (muscle, organs, tumors). Therefore, if skin or subcutaneous tissue must be penetrated to heat deeper tissue, a high and potentially dangerous degree of surface energy deposition would be needed to produce deep heat effectively.

At present, satisfactory heating is limited to depths of 2-3 cm with commercially available diathermy apparatus. In an attempt to overcome this limitation, several investigators have designed specialized equipment in the range of 915 MHz and 2450 MHz microwave bands. However, even with surface cooling, documented temperatures of 42°-44°C have been possible only at 2-3 cm depth, with the thermal gradient continuously decreasing as depth increases. For this reason, clinical trials with standard microwave techniques have been limited to superficial tumors. In an effort to produce deep internal hyperthermia, several approaches have been used, particularly limb perfusion, total body hyperthermia, and combination therapies.

Isolated limb perfusion

In 1967, Cavaliere performed regional limb perfusions with pre-warmed blood at 41.5°-43.5°C in 22 patients with large, recurrent, or single metastatic cancers localized in the extremities. All evidence of gross tumor disappeared in 10 patients, five had regressions, three failed to respond, and four could not be evaluated. The complication rate was high, with six deaths and three immediate amputations; however, massive tumor necrosis was demonstrated (4).

Total body hyperthermia

Pettigrew, in 1974, reported on 38 terminal cancer cases treated by total body hyperthermia at 41.8°C for an average of four hours, which was applied by emersion in molten wax. An objective response, weight gain, or relief from pain, as well as measured tumor regression or histologic evidence of necrosis, was seen in 18 of 38 cases, with four patients dying from disseminated intravascular coagulation (9).

Larkin and Edwards, in 1976, reported their experience with total body hyperthermia applied by a water-circulating suit. Nineteen patients were maintained at 41.5°-42°C for two to five hours, with an objective tumor response noted in 70%. Complications included one death, transient cardiac arrhythmias in 15%, superficial burns in 15%, and transient respiratory distress in 11%, which have been attributed to the seven to eight hours of anesthesia time required to raise and maintain body temperatures in these critically ill patients (11).

Thermoradiotherapy

Hyperthermia has been combined with radiation therapy in the hope of producing a synergistic and augmented response. Since hypoxic cells are more radioresistant than aerobic cells (11), several investigators have concluded that hypoxic cells may be at least as sensitive to hyperthermia as aerobic cells. Others have suggested that the primary effect of hyperthermia is to inhibit cellular recovery from sublethal radiation damage (12).

When tumor cells were exposed to hyperthermia followed by 600 rad radiation, the result was a three-log increase in cells killed as compared to their survival at 37°C to 43°C. Clinical doses for local and regional treatment with the combined treatment may lie in the range of 200-600 rad/fraction (13).

Clinical trials

In 1977, Kim reported his experience using hyperthermia and radiation for cutaneous cancers in man. With fractionated doses of 800-2400 rad followed by 43.5°C surface heating by water bath or microwaves, 7 of 10 patients showed significant prolonged benefits with combination therapy when compared to radiation alone (14).

Hornback has treated 70 patients with advanced malignancy with a combination of microwave (heating) and
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standard radiation. Of 21 patients who received a full course of therapy, 16 (80%) had complete regression of all local tumor, and nine of them remained free of disease from nine to 14 months (15).

The Radiation Therapy Oncology Group has recently established a controlled study among 14 institutions to explore the efficacy of such combined therapy. Phase 1 studies suggest that effective thermal doses are probably in the range of 43°-45°C, combined with higher doses of radiation equivalent to 4,000 rad in four weeks (Boone MLN, Gerner EW, personal communication, 1976).

Thermochemotherapy

The combination of hyperthermia and chemotherapy has also been investigated, since heat is thought to alter tumor cell membrane permeability and enhance uptake of chemotherapeutic agents.

In 1970, Giovanella found a four-log kill in leukemia cells at 42°C in three hours. With the addition of dihydroxybutylaldehyde, a 100-fold kill enhancement was observed with no increase in toxicity. DL-glyceraldehyde, melphalan, sodium oxyamate, and actinomycin-D were also active in combination with heat (16). In vitro data also suggest benefits from hyperthermia combined with Adriamycin (17).

In 1976, Goss reported on the survival of four human fibroblast strains and seven melanoma cell lines after exposure to various concentrations of melphalan alone and in combination with heat at 42°C for four hours. He found that combined treatment was not only synergistic but increased the differential between fibroblast and melanoma lines (18).

When Stehlin, et al treated locally recurrent and intransit melanoma of the extremities using hyperthermic limb perfusion, they found an increased response from 35% to 80% by adding heat (41°C) to melphalan perfusion (19).

Modern Concepts of High-Temperature Local Tumor Hyperthermia

Most studies so far have dealt with moderate hyperthermia of 42°-43°C alone or combined with x-irradiation or chemotherapy, based upon the evidence of selective thermal sensitivity of tumor cells. Lethal temperature/exposure time relationships have been established for many cell lines. However, several investigators have found that at temperatures approaching 45°C a linear kill takes place due to progressive and irreversible protein denaturation. At such high temperatures the differential susceptibility between malignant and normal cells decreases, and host tolerance becomes the prime consideration (1,4,7). Therapeutic hyperthermia in this higher temperature range was not thought feasible until the realization that some solid tumors might act as a heat reservoir and retain heat due to abnormal vascularity and relatively poor blood flow. When Shibata and MacLean evaluated cancers in man, they found that the blood supply was poorer in all tumors studied (21). Using isotope dilution techniques, LeVeen found that tumor blood flow was only 2-15% that of surrounding tissue and concluded that tumors retain more heat than normal tissue whose adaptive vasculature allows heat dissipation (22).

Our evaluation of thermal tolerance on animal skin, extremities, and viscera supported the safety of temperatures of <45°C (23). Interestingly, when normal animal muscle reaches 43°-44°C, spontaneous cooling occurs that maintains the tissue well below its thermal tolerance limit. This phenomenon, which has been observed by others, supports the theory of normal tissue adaptation to hyperthermia that is consistent with augmented blood flow (22). When external, radiofrequency hyperthermia is applied to canine normal viscera, no selective heating of any normal organ occurs.

Animal tumor investigations

Using shortwave-induced hyperthermia, Dickson reported that 7 of 10 rabbits bearing VX2 carcinoma had complete tumor regression with cure of the host. The temperature of skin and normal muscle remained 3°-4°C lower than minimal tumor temperatures, and no injury occurred (23).

In our experience, hyperthermia applied to spontaneously arising dog tumors results in solid tumor heating above 45°C, with normal adjacent tissues remaining at physiologic temperatures. Moreover, when treatment ends, heated tumors dissipate heat much more slowly than adjacent normal muscle, which shows that normal tissues and tumors differ in their capacity to dissipate incident heat.

Human clinical trials

LeVeen applied shortwave hyperthermia to 21 patients and produced tumor temperatures over 46°C, which is 8°-10°C higher than in adjacent normal tissue. Tumor necrosis or substantial regression of cancer was noted in each case with minimal destruction of normal tissue. However, he found that for internal tumors, it was best to transmit energy to lesions that were surgically exposed to avoid heating and occasional burning of surface tissues (22), as others have experienced.

With the specialized radiofrequency instrumentation we have developed to apply hyperthermia at any depth without preferential surface tissue heating, further clinical in-
vestigation of both superficial and deep internal solid tumors is now possible (23-25).

In 30 patients with 36 refractory cancers, we found that intratumor temperatures of 42°-50°C could be achieved in more than three-fourths, with virtually no injury to normal tissues. Selective hyperthermia was possible with both primary and metastatic solid tumors and appeared to be independent of tumor histology. Intratumor heating above 45°C was achieved most often in tumors ≤ 5cm in diameter. Most of the tumors that could not be heated to 45°C displayed physiologic adaptation to heat, similar to that of adjacent normal tissues.

While standard methods of cancer therapy (surgery, x-irradiation, chemotherapy) are most effective for small tumors, our data suggest that hyperthermia may be uniquely effective against larger tumors. Tumor necrosis was marked in lesions heated ≤50°C for 15-60 minutes on one or more occasions. Such treatment caused rapid coagulative necrosis and vascular thrombosis. Superficial tumors generally would slough within several days of therapy. However, effectively heated visceral tumors would remain intact with little change in size and with no evidence of systemic tumor breakdown products by serum creatinine, urate, or urinary protein determinations. Serial biopsies of these internal tumors revealed few functional vessels and progressive tumor replacement by scar. All superficial normal tissues and viscera that were evaluated had the capacity to adapt to heat and, with proper radiofrequency application, could be maintained within a physiologically safe temperature range (23-26).

Hyperthermic immune enhancement

Several investigators have suggested that selective tumor regression after hyperthermia may be due, in part, to some augmentation of the immune system, although few studies are available. Goldenberg found that the growth of human colonic tumors in hamster cheek pouches was inhibited after he applied shortwave diathermy heating; the growth of contralateral, presumably normothermic, cheek pouch tumors was also inhibited (20). Hahn found that sarcomas implanted in mice were highly sensitive to cure by radiofrequency heating. However, cell-kill as assessed by cloning efficiency of treated and immediately excised tumors was insufficient to account for the in vivo cures. This suggested that delayed killing might be the result of stimulation of a tumor-directed immune response, secondary to the direct effects of low or high dose hyperthermia.

Future Prospects

The results of animal research and initial clinical trials, associated with our development of safe and effective equipment, indicate that hyperthermia may become a potentially useful form of local cancer therapy when fully evaluated. Clinical trials are now underway to determine the most therapeutic dose/time regimen, to determine toxicity and therapeutic enhancement ratios of combined chemotherapy and x-irradiation with hyperthermia, and to evaluate any changes in the host immune system with such therapies.

Patients with advanced cancer that resists standard methods of therapy, or those with cancers for which no standard therapy exists, are candidates for experimental hyperthermic therapy.
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