Normal Tissue and Solid Tumor Effects of Hyperthermia in Animal Models and Clinical Trials

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Abstract

Localized hyperthermia therapy by high-energy radio-frequency waves was evaluated in malignant and adjacent normal tissue of 30 patients with 10 types of cancer. Hyperthermia was delivered to superficial and deep visceral cancers in awake patients who had refractory disease. Histological and clinical responses were recorded serially.

Toxicity tests in dogs, sheep, and pigs showed that progressive necrosis of normal and cancer tissue occurred at temperatures above 45°C (113°F). However, as normal tissues approached this temperature, intrinsic heat dissipation occurred (possibly due to augmented blood flow) so that temperatures below 45°C could be maintained, whereas most solid tumors did not have this adaptive capacity and could be heated to 50°C (122°F) with virtually no injury to normal organs, s.c. tissue, or skin. To date, 69 treatments have been administered to 36 tumors in the 30 patients. Selective heating was observed in both primary and metastatic tumors located in surface tissues and internal organs. Response appeared to be related to tumor size in that differential heating was possible more often in the larger lesions. In tumors successfully heated, moderate to marked necrosis occurred.

Radio-frequency hyperthermia appears to be a safe and potentially useful form of therapy for selected cancer patients. While other cancer treatments are more effective for small tumors, hyperthermia may be uniquely beneficial against larger lesions.

Introduction

Most hyperthermic research has concentrated on the tumoricidal effects of heat at 42–44°C, since at these temperatures malignant cells have been found to be slightly more sensitive to heat than are their normal cell counterparts (1–3, 7, 8, 10, 12–14, 17, 20). Higher temperatures may be of greater therapeutic benefit, but above 45°C (113°F), irreversible damage to both normal and neoplastic tissue progresses in a linear dose-time relationship, and host tolerance becomes a limiting factor (2, 5, 8, 9, 19, 20). Recent investigations (11) have suggested, however, that many solid tumors may act as a heat reservoir because their neovascularity is incapable of augmenting blood flow in response to heat. Thus, these tumors may be heated independently above 45°C (Chart 8). Several treatment centers have reported selective heat destruction of tumor by radio-frequency waves (6, 7, 11, 20); however, normal tissue thermal tolerance and local hyperthermic cancer therapy have yet to be tested adequately in animals or humans.

Our study was designed to evaluate the effects of radio-frequency hyperthermia in the range of 42–50°C on both surface and deep visceral normal tissues as well as on spontaneously arising cancers in animals and humans. We present a brief summary of our findings to date to demonstrate that hyperthermia has potential as an effective treatment for many solid tumors without injury to normal tissue. With temperatures at or above 50°C (122°F), marked tumor necrosis has been observed. Implications for human cancer therapy are discussed.

Materials and Methods

The effects of localized hyperthermia on normal skin, s.c. tissue, extremitas, viscera, and spontaneously arising tumors were evaluated in anesthetized large animals. Clinical trials were undertaken in patients with histologically proved cancer who had progressive local or metastatic disease despite all standard forms of therapy (surgery, radiation, chemotherapy, or combination therapy). During all phases of animal investigation and clinical trials, both an oncologist and an electrical engineer were present to evaluate continually the effects of hyperthermia.

Hyperthermia was produced by crystal-controlled radio-frequency waves of 13.56 MHz. A prototype impedance-matching network provided an absorbed power accuracy of >95% at a range of 10 to 1000 watts. Heat was delivered to superficial tumors by contact electrodes, with or without surface cooling. Intrathoracic and intraabdominal heating was achieved using a Magnetrode, a prototype nonsurface contact electrode system of our design created specifically for deep visceral hyperthermia with minimal preferential surface heat absorption.

Temperatures in solid tumors and normal adjacent tissues were recorded serially during brief periods of wave cessation using commercial needle thermistors (Yellow Springs Instrument Co., Yellow Springs, Ohio).

Thermal effects were evaluated by serial clinical examination and needle biopsy. Systemic effects of heat were monitored throughout treatment by changes in pulse, blood pressure, respiratory rate, and core temperature readings. All patients had pre- and posttheraphy complete blood count, differential count, electrolytes, sugar, creatinine, and urate tests, and urinalysis. Patients undergoing deep intrathoracic hyperthermia also had electrocardiogram and cardiac isoenzyme determinations. Patients undergoing deep intraabdominal hyperthermia had liver function and amylase tests. Tumor size was determined by direct measurement, or by radiographs or tomographic scans.
Results

Thermal Response in Normal Animals

Skin. Graded radio-frequency doses of 1 to 10 watts/sq cm applied to canine skin produced occasional transient first-degree burns (erythema) at 42°C, second-degree burns (edema and bullae) at 46°C, and third- and fourth-degree burns (full-thickness skin and muscle necrosis) at and above 50°C (Chart 1).

Extremity. Dog, sheep, and pig extremities were heated deeply to 41–44°C to determine muscle, nerve, and vessel thermal tolerance. At these temperatures, histological examination failed to reveal abnormalities, and in no instance was motor or vascular functional injury apparent over an observation period of 1 to 6 weeks.

Sequential temperature recordings at constant heat dosage showed that when normal muscle reached 43–44°C, abrupt temperature reduction occurred which could not be overcome without a substantial increase in applied heat (Chart 2).

Viscera. Dogs were subjected to graded deep heat, and direct temperature measurements were taken from heart, lung, esophagus, liver, stomach wall, stomach contents (solid and liquid), gallbladder, bile, spleen, pancreas, kidney, small bowel wall and contents, colon, and stoo1 to determine whether or not any particular normal organ was subject to specific heating. It is noteworthy that no preferential heating or "hot spots" occurred at temperatures of 37–49°C.

Dogs were subjected to external hyperthermia equivalent to 42–45°C internal heat dosage for 15 min over the upper chest, lower chest-upper abdomen, and lower abdomen-spinal cord and then observed for 2 to 3 weeks. During this interval, there was no clinical evidence of internal organ injury. Posttreatment cardiac enzymes were transiently elevated, but no abnormalities were apparent by electrocardiogram. Hepatic transaminases and amylase were transiently elevated, but no signs of compromise became manifest. However, prolonged continuous heating at these temperatures universally resulted in fatal cardiac tachycardhythmias.

Thermal Response of Canine Tumors.

Investigation of several spontaneously arising tumors showed that i.t. temperature could be raised to a potentially lethal level while preserving physiological temperature in surrounding normal tissues. Chart 3 illustrates the thermal profile of a sarcoma which occupied two-thirds of a dog’s hemithorax that was heated to 51°C while adjacent normal lung remained at 42.5°C.

Three histologically different tumors were heated to >50°C, and at the termination of radio-frequency hyperthermia, each tumor dissipated heat very slowly when compared to adjacent normal muscle (Chart 4).

Human Clinical Trials

To date, 69 treatments have been administered to 36 tumors in 30 patients with refractory cancer. Tumor heating ≥50°C was observed in 17 of 36 tumors (47%); 45–49°C in 3 of 36 (8%), and 42–44°C in 8 of 36 (22%). In 8 of 36 tumors, (22%), temperatures above 42°C could not be achieved without violating adjacent normal tissue tolerance.

Tumor Histology. Ten varieties of cancer have been evaluated. Selective heating ≥45°C was possible in 20 of 36 tumors (55%), and appeared to be independent of histology (Table 1).

Tumor Size. Selective heating ≥45°C was possible in 43% of tumors ≤5 cm in greatest diameter and in 73% of tumors ≤5 cm (Table 2).

Superficial Tumors. Nineteen tumors arising in skin or s.c. tissue were evaluated, and selective heating ≥45°C was observed in 14 (74%). Temperatures (i.t.) as high as 70°C have been achieved, with up to 57°C at 10-cm i.t. depth. Surface tumors treated ≥50°C for 15 min on one or more occasions generally showed histological evidence of coagulative necrosis and would slough within 10 to 14 days.

Visceral Tumors. Seventeen intrathoracic or intraabdominal tumors have been evaluated. Selective heating ≥45°C was possible in 6 tumors (35%), and all were ≤5 cm in size. Chart 5 illustrates the temperature profile in a patient who had a recurrent 10- x 15- x 30-cm primary intraabdominal sarcoma that progressed despite surgical resection, radiation, and chemotherapy. Chart 6 shows the temperature profile of a 10- x 10-cm hepatic metastasis in a patient with colon carcinoma.

While i.t. temperatures frequently were not uniform, tumors heated ≥50°C for 15 min on one or more occasions generally showed coagulative necrosis and intravascular thrombosis. These tumors usually were replaced by varying degrees of fibrosis with little change in volume (Fig. 1). Occasional central liquefaction was observed.

Toxicity. Hyperthermia generally has been well tolerated in the mildly sedated, awake patient. Normal tissues in the treatment field adjacent to tumors, including skin, s.c. tissue, ab-
diaphoresis, skin flushing, a modest rise in core temperature (0.5—1°C), respiratory rate (2 to 12 rpm), systolic blood pressure (20 to 40 mmHg), and a moderate to marked rise in pulse (20 to 60 beats/mm) (Chart 7).

Nearly one-half of our patients have undergone intrathoracic or intraabdominal hyperthermia with no clinical or laboratory evidence of internal organ injury. No significant arrhythmias, cardiac isoenzyme changes, or abnormal serum parameters of internal organ function have been found at heat sufficient to produce marked tumor heating. No rise in serum creatinine or urate levels was observed in patients with large tumors heated to 45—50°C; therefore, prophylactic i.v. hydration and uricosuric agents were discontinued after initial trials.

Three patients with superficial tumors heated to 50—70°C had slough of immediately adjacent overlying skin; otherwise, injury to normal skin has not been observed. Two obese patients (with 2 to 3 cm of s.c. tissue) had small localized areas of s.c. fibrosis gradually result at temperatures of 42—45°C; otherwise no adverse reactions in normal surface tissues have been observed after deep hyperthermia.

Discussion

Most studies to date have dealt with the effects of moderate hyperthermia in the range of 42—44°C alone or in combination with X-irradiation or chemotherapy, based upon evidence of selective thermal sensitivity of tumor cells in this temperature range (1, 2, 7, 8, 10, 12—14, 17, 20). Lethal temperature-exposure time relationships have been established for many tumor cell lines, and it appears that even higher temperatures may be of greater potential therapeutic value, since the required heating time for tumor destruction is approximately halved (6). However, high-temperature hyperthermia was not considered to be feasible since the differential thermal sensitivity between malignant and normal cells is lost above 45°C, and progressive and irreversible protein denaturation occurs in both normal and malignant tissue (2, 5, 8, 9, 19, 20). Many solid tumors have a relatively poor and physiologically unre-
Selective heating (≥45°C) by tumor type (human)

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of tumors</th>
<th>No.</th>
<th>%</th>
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<tr>
<td>Melanoma</td>
<td>17</td>
<td>9</td>
<td>53</td>
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<tr>
<td>Sarcoma</td>
<td>6</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Colon carcinoma</td>
<td>4</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Epidermoid carcinoma</td>
<td>2</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Teratocarcinoma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36</strong></td>
<td><strong>20</strong></td>
<td><strong>55</strong></td>
</tr>
</tbody>
</table>

Selective heating (≥45°C) by tumor size (human)

<table>
<thead>
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<th>Size (cm)</th>
<th>No. of tumors</th>
<th>No.</th>
<th>%</th>
</tr>
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<td>&lt;5</td>
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<td>9</td>
<td>43</td>
</tr>
<tr>
<td>≥5</td>
<td>15</td>
<td>11</td>
<td>73</td>
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*p = 0.055 (Fisher's Exact Test).

Table 1

Tumor Temperature Decay


Chart 5. Heat profile of primary intraabdominal sarcoma, 10 x 15 x 30 cm, showing selective tumor heating (human).

Responsive blood flow (11, 18), suggesting that tumors might retain more heat than would normal tissue whose adaptive vasculature would allow heat dissipation (15) (Chart 8). On the basis of this hypothesis, several investigators applied radiofrequency hyperthermia and found that while a tumor could be heated to 45–50°C, most normal tissues remained within a physiologically acceptable temperature range (6, 7, 11). However, even with the most sophisticated equipment available, preferential heat absorption occurred within skin and s.c. tissues, which often resulted in injury (6, 11). Thus, virtually no data have been available on the effects of localized deep hyperthermia, and most cancer research has been limited to the study of surface tumors.

Our investigation was designed to evaluate the effects of localized hyperthermia on superficial normal tissues, on visceral organs, and on solid tumors arising in these sites. For this purpose, superficial hyperthermia was applied by various prototype electrodes, with and without surface cooling. Intra-
Heating i.t. above 45°C was achieved most often in tumors ≥5 cm in diameter (Table 2). Most of the tumors that could not be heated to 45°C displayed physiological adaptation to heat similar to that of adjacent normal tissues. Thermal adaptation was most often observed in lesions <5 cm in size, and rarely in lesions ≥5 cm, probably due to a diminished vascular integrity in the larger tumors. While standard methods of cancer therapy (surgery, X-irradiation, and chemotherapy) are most...
effective for smaller tumors, our data suggest that hyperthermia may be uniquely effective against larger tumors.

Tumor necrosis was marked in lesions heated ≥50°C for 15 to 60 min on one or more occasions. Such treatment caused rapid coagulative necrosis and vascular thrombosis (Fig. 1, A and B). Superficial tumors generally would slough within 10 to 14 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 (Fig. 1C), as others have noted (16). We postulate that the attendant vascular necrosis and thrombosis which occur at these high temperatures prevent absorption of the tumor and allow only fibrous replacement over a prolonged interval. Therefore, direct biopsy rather than size measurement appears to be necessary to assess therapeutic benefit in visceral cancers treated by hyperthermia.

Radio-frequency hyperthermia with an absorbed power density to 1000 watts generally was well tolerated in our patients, with virtually no normal tissue injury. Our patients appeared to dissipate localized heat by evaporation (diaphoresis) and increased peripheral blood flow (flushing and pulse rise), rather than by increased ventilation (Chart 7).

All superficial normal tissues and viscera that were evaluated had the capacity to adapt to heat and, with proper radio-frequency application, could be maintained within a physiologically safe temperature range. Slough of normal skin overlying superficial tumors that were heated to 50—70°C was probably due to the extremely poor vascularity of such tissue.

The results of our 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. We are also investigating toxicity and therapeutic enhancement ratios of combined chemotherapy and X-irradiation with hyperthermia, as well as any changes in the host immune system with such therapies. At present, we do not regard hyperthermia as an appropriate alternative to any modality to consider when other modes fail.

Acknowledgments

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References

Fig. 1. Photomicrographs of human intraabdominal sarcoma treated 5 times at ≥50°C for 15 to 30 min. A, pretreatment, showing pleomorphic, hyperchromatic nuclei, prominent nucleoli, moderate amounts of cytoplasm, scant amounts of supporting tissue, and intact vessels; B, at 2 weeks, showing coagulation necrosis and vascular thrombosis; C, at 3 months, showing marked fibrosis, tumor cell ghosts, and obliterated vascular channels. H & E, × 100.
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