Clinical Use of Thermal Enhancement and Therapeutic Gain for Hyperthermia Combined with Radiation or Drugs

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Abstract

Values for thermal enhancement and therapeutic gain are useful for deciding future directions of hyperthermia combined with other cancer therapy modalities. Evidence of thermal enhancement of effects on normal tissues is important as it indicates the need for dose modification. Specific values cannot be used generally to determine the dose degree of modification for clinical applications. A range of values accounting for many variables, including method of dose delivery for heat and the other modalities and knowledge of the normal tissues at risk, would be required for such specific application. There is frequently hyperthermic enhancement of radiation damage to acutely responding tissues. That may be avoided if tumors can be selectively heated, but extensive temperature monitoring is necessary to avoid hot spots. Irradiation and heating of spontaneous canine tumors resulted in an increased probability for tumor control with no apparent increase in late complications. Human clinical studies have shown that, with care, tumor response can be enhanced without significantly increasing normal tissue damage and that a therapeutic gain can be achieved. Caution must be exercised because, with few exceptions, follow-up was not long, and the tissues at risk were limited. Most human studies have been of relatively superficial tumors of small volume. Little information is available on whole-body or regional hyperthermia for assessment of thermal enhancement or therapeutic gain. Also, there is little information about chemotherapy combined with heat, although studies of heat with perfusion chemotherapy for malignant melanomas of the extremity have shown significantly increased survival rates.

Introduction

The objective of new modalities for cancer treatment is to improve control of the disease while maintaining a good quality of life. The need for assessment of quality of survival as well as measuring survival rates has been stressed by radiation oncologists (35, 44). Enhancement of tumor control must be considered in conjunction with the maximum acceptable probability of complications to determine a therapeutic gain.

Hyperthermia is one of several methods considered in recent years to improve tumor control. Surgery and radiation therapy provide limited control for deep-seated tumors in several anatomical sites. There are also more accessible tumors which recur locally following irradiation or surgery for which improved control rates could be achieved (41). Clinical interest in hyperthermia increased, based on experiments indicating an enhancement of tumor control in rodents when heat was combined with radiation or chemotherapy (8, 16, 27, 34, 42). Human clinical studies also have shown that the addition of heat to radiation tends to enhance tumor control for short intervals following treatment (3, 7, 23, 25, 26, 28, 30, 45). Thermal enhancement of tumor regression was observed, and there were few complications, so there appeared to be a therapeutic gain. The observations have not been sufficiently long to evaluate either long-term control or late complications.

TER and TGF

Robinson et al. (34) were among the first to use TER for comparing response of mouse tumors and skin to heat plus radiation to the response to radiation alone. They showed that a greater TER could be achieved for mouse tumor than for mouse skin. They defined TER as the ratio of radiation sensitivity at 37.5° to the sensitivity at an elevated temperature. They obtained the TER as follows:

\[ \text{TER} = \frac{\text{Radiation dose for a specified effect}}{\text{Radiation dose with heat for a specific effect}} \]

When they heated mouse mammary tumors and normal skin in water bath temperatures of 43° for 1 hr and irradiated in the middle of the heat interval, they obtained a therapeutic gain of 2.1. They divided the TER for tumor by the TER of skin to obtain what they termed the therapeutic ratio. Subsequently, the term TGF has been used for the value obtained as follows:

\[ \text{TGF} = \frac{\text{TER for tumor}}{\text{TER for normal tissue}} \]

TGF has been calculated for some mouse tumors, but the values are much more difficult to obtain from human clinical trials (14, 18).

Thrall et al. (43) also reported response of combined heat and irradiation on mouse tumor systems. In those studies, thermal enhancement was shown for both skin and tumor. A therapeutic gain was achieved only for irradiation under hyperbaric conditions immediately before heating. In those studies, heating was in a water bath at 44.5° for 15 min. Irradiation was given either immediately before or after heating. Irradiation after heating caused much greater damage to skin. In a study of a very radiation-sensitive osteogenic sarcoma of mice, tumor control was achieved without skin damage, regardless of the sequence of heating and irradiation (15). The total dose was only 600 rads given in 3 fractions. At the time of those earlier papers, it was not clear that the variables of temperature, time, and sequencing would significantly affect thermal enhancement and therapeutic gain.

1 Presented at the Workshop Conference on Hyperthermia in Cancer Treatment, March 19 to 21, 1984, Tucson, AZ. This work was supported in part by USPHS Grant CA29582, Department of Health and Human Services.
The paper of Robinson et al. (34) was one of the few indicating a therapeutic gain, and even in that work, the radiation dose required to produce the specified level of skin damage was slightly less than for tumor control. Therapeutic gain was a useful term, because values greater than 1 indicated greater relative effect on tumor than on skin. Skin response had been established as a standard method for comparison and was convenient (4). It was not known then, as now, what tissues might be dose limiting, as that would depend on the sites chosen for hyperthermic therapy. Skin is a reasonable comparative tissue for oral mucositis and intestinal damage but does not predict for late effects (47, 49). Late-effects studies must be done on the specific tissue of concern as the level of acceptable toxicity, sensitivity, and time of appearance of lesions vary among tissues.

The term "therapeutic ratio" is sometimes used for comparing different treatment methods. It has limited meaning in cancer therapy, because maximum tolerated doses are routinely used. For some other diseases, the dose of the therapeutic agent needed to control the disease is much less than that accompanied by significant toxicity. A therapeutic ratio or index generally is obtained by dividing the dose accompanied by an acceptable level of toxicity by that which will control the disease. The therapeutic ratio is one for radiation therapy and is not likely to change. For most radiation therapy, the maximum dose is given which is accompanied by an acceptable probability for complications, and there will be a varying probability for tumor control. If a new method of therapy were developed which is more effective, the doses would probably be given to the same level of acceptable toxicity. The important change would be an increased percentage of tumor control.

### Therapeutic Gain with Heat and Radiation of Human Tumors

Most of the human clinical trials have shown thermal enhancement of tumor response. Normal tissue damage was more difficult to evaluate in humans as the trials were designed to avoid significant damage to normal tissues. The following reports were chosen for discussion, because the studies were designed prospectively to compare heat and radiation with radiation alone, so that thermal enhancement and, in some cases, therapeutic gain could be determined.

Chang et al. (6) listed some of the limitations encountered in RTOG Phase 1 trials. Thermal enhancement values for tumors frequently could not be obtained because of insufficient survival time or the failure of at least one lesion to regrow. Thermal enhancement for tumors was evaluated from regrowth data. Thermal enhancement for skin response could not be determined adequately if the lesions were in different anatomical sites. In a continuation of that study, a therapeutic enhancement of 2 was obtained for tumors, based on early complete tumor responses (37). Those studies were done with standard fractionation radiation therapy and hyperthermia given 30 min following radiation. The interval between heat treatments was at least 72 hr. At the 6-month follow-up, the therapeutic enhancement ratio for 35 patients stabilized at approximately 1.3 (Table 1). That value was maintained in 20 patients for 12 to 18 months after therapy. For the 18 of 20 patients who had 2 lesions, one lesion was treated with heat and radiation, and the other lesion served as a radiation-only control. The authors stated that no long-term toxicity due to hyperthermia was observed. For the RTOG 77-10 protocol reported by Scott et al. (36), a thermal enhancement value of 2.2 was given for tumors. They stated that this greater thermal enhancement was obtained because the radiation therapy was not definitive and was applied as palliation for patients known to have limited survival because of metastases. The second protocol, RTOG 78-06, was devised in which patients were given definitive radiotherapy to which hyperthermia was added. There was less thermal enhancement in the second

### Table 1
**Thermal enhancement and therapeutic gain with radiation and hyperthermia of human tumors**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Tumor type and site</th>
<th>Heat treatment</th>
<th>No. of heat treatments</th>
<th>Sequence of Δ and XRT</th>
<th>Radiation fraction size (Gy)</th>
<th>Total dose (Gy)</th>
<th>Thermal enhancement gain</th>
<th>Therapeutic gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott et al. (36, 37)</td>
<td>Superficial epithelial tumors including melanomas</td>
<td>42.5°–43.5°/45 min (Accelerated schedule)</td>
<td>12</td>
<td>2 Δwk 30 min after XRT</td>
<td>1.8–2.0</td>
<td>50–60</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>Kim et al. (20)</td>
<td>Recurrent melanomas; s.c. and lymph nodes</td>
<td>42.0°–43.5°/30 min for all protocols</td>
<td>13</td>
<td>2 Δwk immediately before XRT</td>
<td>3.3</td>
<td>42.9</td>
<td>2.3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>2 Δwk immediately before XRT</td>
<td>4</td>
<td>40</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>1 Δwk immediately before XRT</td>
<td>5.5</td>
<td>38.5</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>1 Δwk immediately before XRT</td>
<td>6.6</td>
<td>39.6</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Arcangeli et al. (1)</td>
<td>Neck node metastases of carcinomas</td>
<td>42.5°/45 min</td>
<td>7</td>
<td>3 Δwk immediately after XRT (Accelerated schedule)</td>
<td>1.5–2.0</td>
<td>60</td>
<td>1.74</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Various superficial recurrent tumors</td>
<td>42.5°/45 min</td>
<td>8</td>
<td>2 Δwk immediately after XRT</td>
<td>5</td>
<td>40</td>
<td>2.05</td>
<td>1.78</td>
</tr>
<tr>
<td></td>
<td>Various superficial recurrent tumors</td>
<td>42.5°/45 min</td>
<td>8</td>
<td>2 Δwk 4 hr after XRT</td>
<td>5</td>
<td>40</td>
<td>1.79</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>Various superficial recurrent tumors</td>
<td>45.0°/30 min</td>
<td>6</td>
<td>2 Δwk immediately after XRT</td>
<td>6</td>
<td>30</td>
<td>2.63</td>
<td>1.25</td>
</tr>
</tbody>
</table>

* Δ, heat; XRT, radiation.
study, which was not due to less satisfactory results from hyperthermia but the result of more effective radiation therapy in the patients treated only with irradiation. There was no observed increase in toxicity from the addition of hyperthermia. That was an important observation, because heat had been added to a full course of radiation therapy.

One of the earlier reports was of the use of temperatures of 41 to 43.5°C for 30- to 90-min sessions combined with radiation therapy (19). A variety of tumors was included. When comparing complete response of tumors which were treated with heat and irradiation to those which received radiation alone, a thermal enhancement of 3 was obtained. Enhanced skin reactions were only in areas where there was previous scarring, skin grafting, or when fractionated doses in excess of 5 Gy per session were used.

In a later paper by that same group, more than 100 lesions in 38 patients were treated with radiation alone and hyperthermia combined with radiation (20). Most of the lesions were treated once or twice a week. The tumor control rate for an unspecified period of time was 75% for radiation combined with heat and 46% for radiation alone. A thermal enhancement of 1.5 could be obtained from those data. Minimal normal tissue response was observed. The values for thermal enhancement for human tumors are usually derived from comparisons of percentages of tumor response and are not ratios of doses as defined earlier for TER.

Arcangeli et al. (1) reported the results of treatment of 57 patients, each having at least 2 lesions. A total of 123 lesions was treated with either radiation alone or radiation combined with hyperthermia. Three main studies were carried out. The first was done on 26 patients with a total of 52 neck node metastases from head and neck carcinomas. Irradiation was combined with hyperthermia of 42.5°C for 45 min. Although the radiation fraction sizes were small, they were given on an accelerated schedule. Three doses per day were given of 2, 1.5, and 1.5 Gy with a 4-hr interval between fractions. These were given 5 days a week for a total dose of 60 Gy. For that group of patients, heat was applied immediately after the second daily fraction of irradiation every other day for a total of 7 sessions. In another study, 5 Gy per fraction were given twice a week at intervals of 72 to 96 hr for a total dose of 40 Gy. A variety of recurrent tumors was treated, including melanomas, carcinomas, and undifferentiated lung tumors. Hyperthermia of 42.5°C for 45 min was given immediately or 4 hr after irradiation. For a third study, 5 fractions of 6 Gy were given twice a week at intervals of 72 to 96 hr up to a total of 30 Gy and combined with temperatures of 45°C for 30 min applied immediately after each radiation fraction. A variety of tumors as in the second group was treated. A TEF was obtained. They stated that a TEF was usually defined as the ratio of thermal enhancement of tumors to the thermal enhancement of skin. As they used only one radiation dose level, they used thermal enhancement as defined by the ratio of the percentage of response, which was either tumor clearance or moist desquamation, after combined modality to the percentage of response after a single treatment modality. Using those values, a TEF of 1.58 was obtained with conventional fraction sizes of radiation and what they termed moderate heat (Table 1). TEF values of 1.4 and 1.5 were observed after the second trial in which high fraction sizes of irradiation were combined with the delayed or immediate moderate hyperthermia. The highest TEF value of 2.1 was obtained with large fraction sizes followed immediately with hyperthermia of 45°C for 30 min. In that case, they were able to preferentially heat the tumor and used active skin cooling. They stated that tumor control increased with both radiation fraction size and temperature. They suggested that, if radiation therapy had never been given before, an optimal treatment would result by adding 5 to 7 immediate or delayed sessions of hyperthermia of 43°C for 45 min once or twice a week. That would be added to a full conventional fractionation or hyperfractionation radiotherapy course. They felt that no increase of radiation damage to normal tissue would result, particularly if tumor could be selectively heated. In heavily irradiated tissues or when rapid treatment of several lesions was required for palliation, an optimal treatment would result by using 5 to 7 fractions of 5 or 6 Gy in combination with 5 to 7 hyperthermic sessions given twice a week.

Arcangeli et al. (1) pointed out the important differences in thermal enhancement between experimental animal data and those obtained in humans. Most of the human studies were not done as radiation dose-response assays as are done in experimental animals. Therefore, the thermal enhancement is taken as the ratio of response to a given radiation dose. That value does not represent a true dose-modifying factor and may be considerably greater than a TER, which is based on a uniform biological response. In experimental animals, a dose-response assay is usually done, and TERs as defined by Robinson are determined from the doses to cause a given level of effect.

Dewhirst et al. (9) were faced with this problem in analyzing data from a trial in spontaneous tumors in dogs and cats. They used a value which they termed the TRR. They chose that term because the study was designed to compare a constant irradiation protocol with that same protocol combined with heat. The TER was obtained by dividing the percentage of response of tumors to heat and irradiation by that for radiation alone. They treated 130 pet animals with squamous cell carcinomas, melanomas, fibrosarcomas, mammary adenocarcinomas, and mast cell sarcomas. They attempted to heat tumors to 44°C ± 2°C for 30 min. The radiation dose was 460 rads per fraction twice a week for 8 fractions. The heat was given once a week immediately following radiation. The TRR for all tumors treated was 2.3. These data have subsequently been analyzed to show the important influence of histology, volume, site, and heat treatment method (10, 11). The aspect of greatest importance was the minimum tumor temperature. This seemed to govern the biological response to combined heat and radiation.

Dose-response studies provide data which can be used to obtain a dose-modifying factor which for heat is called the TER. A collaborative study at Colorado State University and the University of Arizona was designed to determine TER and TGF for spontaneous tumors in dogs. Preliminary results have been obtained for squamous cell carcinomas of the oral cavity of dogs. Dogs were randomized to receive radiation only or radiation plus heat. They were also randomized to one of 4 radiation doses within each group. The total radiation doses were divided in 10 fractions given 3/week for 3 weeks. Heating was done twice a week with a 72- or 96-hr interval between. A minimum tumor temperature of 42°C for 30 min was produced by radiofrequency, microwave, or ultrasound equipment. Data were obtained from dogs followed for at least 1 year. The curves for radiation only were redrawn from a previous dose-response assay of oral...
Clinical use of TGF will depend on tumor type and location among other things. Normal tissue tolerance varies considerably. As pointed out by Withers and Peters (48), it is influenced by the tissue being irradiated, the treatment volume, fractionation pattern, the definition of a complication, the attitude of the therapist, and other clinical variables. Depending on these variables, several levels of complications might be acceptable. Some complications are totally unacceptable, e.g., spinal cord necrosis. Perhaps a low incidence of medium severity complications, such as mandibular necrosis, might be warranted if there is a high rate of uncomplicated tumor control. A high probability of nondebilitating complications, such as apical lung fibrosis, might be acceptable if demanded for higher tumor control. Therefore, the clinical definition of tolerance is a dose regimen producing the maximum acceptable probability of complications necessary in a given treatment situation.

The levels of complications and associated tumor control are shown for tumors of the oral cavity of dogs (Chart 2). The complication curve is for bone necrosis. If normal tissue complications are to be avoided, the probability for tumor control would be low. In the example given, the tumor control probability would be only 30% for 35 Gy. At 40 Gy, the tumor control probability would be about 65% with normal tissue complications less than 5%. To achieve a 90% tumor control probability, a complication rate of about 65% would have to be accepted.

If hyperthermia causes the tumor control curve to shift to the left as in Chart 1 with no accompanying shift in the normal tissue curve, a 90% tumor control probability could be achieved with a very low probability for complications.

Hyperthermia and Drugs

There is far less information on hyperthermia combined with chemotherapy than with radiation. The combination of hyperthermia plus irradiation is complicated by many variables, and the combination of hyperthermia with drugs is even more complex because of the pharmacokinetics and varying toxicity associated with each drug. A few reports of human tumor response indicated an advantage to be obtained from this method (33, 38, 39).

Stehlen (38) used chemotherapy and heat for treatment of...
melanomas for several years. He used melphalan perfusion with regional hyperthermia at temperatures up to 40° for 2.5 hr. The 5-year survival increased from 22 to 77% when heat was added to perfusion. In a more recent study of perfusion chemotherapy for Stage I malignant melanomas of the extremity, hyperthermia combined with chemotherapy was compared to more conventional surgical methods (33). The survival rates for clinical Stage I patients at 5, 10, and 15 years were 91, 86, and 77%. The disease-free survivals for those same periods were 85, 80, and 80%. These values were significantly better than the surgical controls. Fifteen % of the patients failed the perfusion treatment compared to 33% in the control group. Two major complications occurred. One patient perforated an ulcer of the upper gastrointestinal tract, and another developed a gangrenous foot requiring above-the-knee amputation. The authors stated that no significant drug toxicity occurred. As there were no controls for perfusion without heat, a thermal enhancement of therapeutic efficacy could not be determined.

Thermal enhancement for whole-body hyperthermia is even more difficult to evaluate. Those patients usually have widely disseminated disease. In a recent report of 27 patients treated with whole-body hyperthermia in combination with either chemotherapy or radiotherapy, there was an improved therapeutic effect in 6 of the patients (46). It was stated that toxicity, such as liver damage and respiratory problems, was considerable, and there were 2 fatalities. Most reports indicate that whether whole-body hyperthermia is used alone or combined with chemotherapy, it results in only transient responses (2, 5, 22, 29, 32).

Another area of interest in the combination of hyperthermia and chemotherapy is in treatment of bladder carcinoma (17, 21). Bleomycin with warm 0.9% NaCl solution (saline) at 43 to 45° has been used (21). Recurrence of disease was frequent in many patients who had complete remissions. Of a total of 33 patients, there were complete responses in 14 patients. It was felt that these responses may be longer term because the study also included a 4-week exposure to 35 to 40 Gy for treatment of transitional cell carcinomas of the bladder, which was also irrigated with a solution of warmed saline which contained bleomycin (30 mg/ml).

Some of the problems which have prevented more widespread use of hyperthermia with chemotherapy have been discussed (24). A suggestion was that, while the radiation therapist might more readily accept use of the necessary equipment, the chemotherapist would be more comfortable trying another drug combination than adding the unknown complications of heat. There is also far less preclinical information on the interaction of hyperthermia and drugs than with radiation. Much work needs to be done on the effects of local and whole-body hyperthermia on pharmacokinetics and toxicity.

Summary

Far more work has been done with the combination of hyperthermia and radiation than with drugs. The main complications reported have been thermal burns due to excessive heat from applicators at some surface point. The reports have criticized the inability of available equipment to produce uniform deep hyperthermia and emphasized problems with thermometry. Given those limitations, there is reason for optimism for the combined use of heat and radiation. No increased incidence in serious late complications has been observed in the somewhat limited duration human studies or in the longer-term large-animal studies specifically designed to evaluate for late complications. It appears that thermal enhancement of tumor response can be obtained with a relatively low risk of increased complications. For the most part, relatively superficial tumors and small treatment volumes have been evaluated. The true thermal enhancement and therapeutic gain will be obtained only after many years of clinical observations in which tumors of similar stages, locations, and histology will be compared with ongoing evaluations of more conventional treatments. The thermal enhancements reported are often modest but could still lead to a significantly increased number of tumors for which local control is achieved (Table 1).

A major objective of hyperthermia has been to achieve control of some deep-seated tumors that currently are difficult to control. Until effective methods for deep heating and thermometry are obtained, this may be difficult to do. It may be possible to use whole-body hyperthermia for uniform temperature control and use that in combination with either radiation or chemotherapy. In the meantime, if hyperthermia is to be used to improve clinical control rates, it may necessarily be limited to relatively superficial tumors. That could also be an advantage in that there are significant numbers of local failures following conventional treatment. In addition, hyperthermia may be used for retreatment of tumors which have failed conventional radiotherapy. The clinical data suggest that most methods of treatment can achieve a minimum tumor temperature of 42°. With care, it is possible to prevent heating of surrounding normal tissues. Where that is possible, there should be a significant enhancement of response to radiation without an increase in probability of serious complications.

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