The Utility of Thermal Dose as a Predictor of Tumor and Normal Tissue Responses to Combined Radiation and Hyperthermia

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Abstract

A total of 236 dogs and cats with a variety of cancers were randomized to receive radiation (XRT) or heat plus XRT. In those tumors which were heated, thermal gradients developed which varied in temperature minima and maxima. The influence of the thermal gradient characteristics on tumor and normal tissue responses was examined by correlation of response with the magnitude of gradient minima and maxima. Using multivariate analysis, the influence of other factors such as tumor histology, volume, site, heat treatment method, and number of heat fractions on tumor response was examined.

Of all factors examined, tumor volume and non-site-specific average minimum equivalent min at 43°C emerged as consistent predictors of both complete response rate (p < 0.001) and duration response (p < 0.05).

No significant enhancement of moist desquamation or late fibrosis was seen for heat + XRT versus XRT alone. The incidence of direct thermal injury to skin was positively correlated with maximum intratumoral equivalent min at 43°C. These results indicate that a therapeutic gain is achievable with heat + XRT, but successful application of the therapy is dependent on achieving high tumor thermal gradient minima and low maxima.

Introduction

Most human studies examining the effectiveness of heat and XRT have had favorably high CR rates for a variety of tumor histologies and volumes. The results have been surprisingly consistent in spite of wide variations in hyperthermic devices, durations of heating, and sequencing between heat and XRT (2, 16, 22, 23, 25). Matched lesion studies have consistently shown a 2-fold increase in CR rates for the combined modality versus XRT alone (1, 6, 19, 24, 29, 31). Similar improvements in CR rates have been observed in pet animal tumors (9).

The clinical reports have been encouraging in spite of the fact that current methods of heat delivery are far from ideal. Target tumor temperatures are difficult to achieve and measure. Several investigators have reported that thermal gradients can be quite large, even for peripherally accessible tumors (20, 23, 25, 31). The size of the thermal gradients has been related to the characteristics of the heating technique, efficiency of coupling to tissue, and tissue blood flow. Both tumor volume and site have also been shown to influence thermal gradients, probably because they indirectly interact with power deposition patterns (10, 11, 23, 25).

Biologically, the intratumoral thermal gradients would be expected to influence tissue responses to the modality since hyperthermic damage is known to be related to both temperature and time. In rodent models, nonuniform temperatures have been related to variability in normal tissue and tumor responses to heat alone and heat plus XRT (14, 17, 32). In clinical studies of heat + XRT, temperature gradient minima have been related to CR rates (10, 23) and duration of response (10). Average temperatures have not correlated well with tumor response (10, 20, 23, 25). Temperature gradient maxima have been positively (19) and inversely correlated with response (10).

Thermal enhancement of XRT-induced normal tissue effects has not been a significant problem in almost all studies reported. In many of these, the total radiation dose received was relatively low (6, 19–22, 25, 31). However, even in studies where near tolerance levels of XRT have been used, little or no enhancement of XRT effects has been observed (1, 29). Enhancement of XRT effects has been observed in patients treated with 4-Gy fractions as opposed to 2-Gy fractions (1).

Direct thermal damage to normal tissues has been reported by most investigators. The frequency of serious thermal injury has been low, however (21–23, 25). The relatively low incidence of this type of injury can be attributed to the facts that active cooling of adjacent normal tissues is usually performed, and most patients are awake and can provide feedback to the therapist when tissues become excessively hot. In most studies, no correlations have been attempted between the incidence of thermal injury and measured temperature. In one report, however, the incidence of burns and blisters was positively correlated with intratumoral temperature maxima (20).

The purpose of this report is to update our clinical experience in a Phase III trial of pet animal cancers treated with either XRT alone or heat + XRT. The emphasis will be on the influence of thermal gradients on both tumor and normal tissue responses to heat + XRT. The influence of other variables such as tumor histology and volume will also be presented.

Materials and Methods

Animal Patients. Dogs and cats with spontaneous cancers were referred to our tumor clinic from practicing veterinarians. They either had no prior treatment, were postsurgical recurrences, or had residual microscopic disease following attempted surgical extirpation. Animals with heat-accessible tumors, no distant metastases, and no serious concomitant health problems were acceptable for randomization.

Protocol. The animals were stratified by histological type and randomized to receive XRT alone or heat combined with XRT. The prescribed XRT dose was 460 rads/fraction, twice weekly for 8 fractions. One heat fraction/week was scheduled. When heat was applied, it preceded XRT by no more than 10 min. Every attempt was made to raise tumor temperatures to a minimum of 42.0°C. The target temperature was 44°C. The duration of heating was 30 min from steady state.

1 Presented at the Workshop Conference on Hyperthermia in Cancer Treatment, March 18 to 21, 1984, Tucson, AZ. This work was supported by Grants CA 17343 and CA 30774 from the National Cancer Institute, NIH.
2 To whom requests for reprints should be addressed at: Duke University Medical Center, Radiation Oncology, Box 3085, Durham, NC 27710.
3 The abbreviations used are: XRT, radiation; CR, complete tumor response; Eq43, equivalent min at 43°C; TRR, thermal relative risk; RRR, relative relapse rate.
Treatment Methods

Radiotherapy. Animals were anesthetized with halothane following preanesthetization with atropine sulfate (0.05 mg/kg) and induction with thiopental sodium (10 to 20 mg/kg). XRT treatments were given using linear accelerators with X-ray energies of 4 or 10 MeV and electron energies of 6, 9, 12, 15, and 18 MeV (Clinac 18 or 4; Varian Associates, Inc.). Orthovoltage X-rays were also used with energies varying from 60 to 300 kVp (Siemens Stabilipan). The details of these approaches have been published previously (9).

Hyperthermia. Heat treatments were given using 500-kHz high-frequency current or 2450-MHz microwaves. Intratumor temperatures were monitored using calibrated 26-guage needle thermistors (Yellow Springs Instrument Co., Model 524) (4). Three to 10 thermistors were placed in a repeatable geometric array within the heated volume. They were placed at right angles to the electric field in order to minimize artifact. Measurements were made with power off for microwaves. Power downs were not done for 500-KHz high-frequency heating unless artifact was verified. When possible, thermistors were placed in the same regions for successive heatings. The details of these heating and thermometry techniques have been published elsewhere (5, 9, 10, 12).

An illustration of how the thermometry data was summarized is described below. For each heat treatment, a family of time-temperature curves was obtained which clustered around the prescription of 44°C. This family of curves represented the measured thermal gradient which existed within the tumor (Chart 1). The time-temperature curve for each thermistor was converted to $Eq_{43}$ using the method of Sapareto (28). The form of the relationship is

$$Eq_{43} = (\Delta T)^{0.5}$$

where $\Delta T = 5$ min and $R = 0.25$ when $T < 43.0^\circ$ and 0.5 when $T \geq 43^\circ$.

Times for temperatures below $38^\circ$ were assumed to contribute 0 $Eq_{43}$.

From summary data such as that shown for the sample case, intratumoral minima for each treatment, site specific average minima, and non-site-specific average minima and maxima were identified (Table 1). All animals were scheduled to receive 4 heat treatments. In some cases, less than 4 treatments were given either as a result of equipment availability, sloughing of tumor, or toxicity. Therefore, the actual number of heat treatments delivered was documented. Each of the above parameters showed a distribution of values when looking at the whole population of animals; e.g., the range of $Eq_{43}$ for intratumoral minima on the first treatment was from 0 to 182, with a mean of 16.7 $Eq_{43}$, while the range for the non-site-specific minimum went from 0 to 153, with a mean of 17.6 $Eq_{43}$.

Response End Points

Follow-up examinations were done at our institution at monthly intervals after therapy completion. Responses of 1-month duration or more were categorized as: (a) CR, complete regression of all clinically detectable disease; (b) partial response, with at least 50% reduction in tumor volume; and (c) no response, with less than 50% volume reduction or continued growth. A recurrence was defined as at least a 25% increase in tumor volume over the smallest posttreatment volume or reappearance of primary tumor following a CR. All recurrences were verified by biopsy. Stable partial responses of a duration of more than 1 year were incisionally biopsied. If there was no evidence of tumor, they were reclassified as a CR.

Normal tissue effects were classified as shown in Table 2. The worst effect observed was recorded on each treatment day and on all follow-up examinations. Care was taken to record radiation and heat effects separately. This distinction was not difficult, except in the case of those

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**Table 1**

<table>
<thead>
<tr>
<th>Description</th>
<th>Probe</th>
<th>Treatment 1, $Eq_{43}$</th>
<th>Treatment 2, $Eq_{43}$</th>
<th>Treatment 3, $Eq_{43}$</th>
<th>Treatment 4, $Eq_{43}$</th>
<th>Site-specific av., $Eq_{43}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal</td>
<td>1</td>
<td>94.5</td>
<td>106.9</td>
<td>9.5</td>
<td>45.6</td>
<td>64.1</td>
</tr>
<tr>
<td>Ventral</td>
<td>2</td>
<td>221.8</td>
<td>112.8</td>
<td>3.5</td>
<td>43.9</td>
<td>95.4</td>
</tr>
<tr>
<td>Medial</td>
<td>3</td>
<td>34.4</td>
<td>49.1</td>
<td>43.5</td>
<td>82.7</td>
<td>52.4</td>
</tr>
<tr>
<td>Lateral</td>
<td>4</td>
<td>77.7</td>
<td>36.8</td>
<td>182.6</td>
<td>144.7</td>
<td>105.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per treatment minimum (from above)</td>
<td>34.4$^a$</td>
<td>36.8$^a$</td>
<td>3.5$^a$</td>
<td>43.9$^a$</td>
<td>29.8$^a$</td>
<td></td>
</tr>
<tr>
<td>Per treatment maximum (from above)</td>
<td>221.8</td>
<td>112.8</td>
<td>182.6</td>
<td>144.7</td>
<td>160.4$^a$</td>
<td></td>
</tr>
</tbody>
</table>

* $^a$ Treatment 1 data were extracted from Chart 1 as described in the text.

* $^b$ These gradient descriptors were individually examined for their correlation with tumor and normal tissue response, as described in the text.
Table 2

Classification of normal tissue effects

<table>
<thead>
<tr>
<th>Radiation effects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (skin)</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Pigmentation change</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
</tr>
<tr>
<td></td>
<td>Dry desquamation</td>
</tr>
<tr>
<td></td>
<td>Moist desquamation</td>
</tr>
<tr>
<td></td>
<td>Ulceration</td>
</tr>
<tr>
<td></td>
<td>Deep tissue necrosis</td>
</tr>
<tr>
<td>Late (skin)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Mild fibrosis with visible scar</td>
</tr>
<tr>
<td></td>
<td>Moderate fibrosis with palpable thickening of skin</td>
</tr>
<tr>
<td></td>
<td>Severe fibrosis with interference of function</td>
</tr>
<tr>
<td></td>
<td>Nonhealing skin ulcer, persistent for ≥ 6 mo</td>
</tr>
<tr>
<td>Bone and/or soft tissue</td>
<td>Necrosis following latent period</td>
</tr>
<tr>
<td>Heat effects</td>
<td>Erythema and edema, first degree</td>
</tr>
<tr>
<td></td>
<td>Blister, second degree</td>
</tr>
<tr>
<td></td>
<td>Full-thickness skin necrosis, third degree</td>
</tr>
<tr>
<td>Infarct</td>
<td>Skin normal at end of treatment; well circumscribed</td>
</tr>
<tr>
<td></td>
<td>Loss of blood supply develops ≥ 48 hr after therapy</td>
</tr>
</tbody>
</table>

Persistent ulcers which originally developed as a result of thermal injury. Those were coded under late radiation effects.

We examined other normal tissue effects, including permanent epilation, neuropathies, mucositis, and development of periodontal disease. For the sake of brevity, these side effects will not be discussed in detail in this paper.

Statistical Methods

Initial response (CR rate) was examined for each variable separately with \( \chi^2 \) tests (30). Multivariate analysis for CR rates was done using a logistic regression model (7). The method models the logit of the CR rate \( \logit(\frac{p}{1-p}) \) as a linear function of the independent variables.

Univariate analysis of response duration was done using Kaplan-Meier or product-limit survival curves (18) which were then tested for statistical differences by both logrank (26, 27) and Wilcoxon statistics (3, 13). Multivariate analysis of response duration was done using a proportional hazards regression model (8).

Results

Animal Patient Population. A total of 166 dogs and 70 cats with either mast cell sarcomas (46), mammary adenocarcinomas (32), malignant melanomas (32), squamous cell carcinomas (82), fibrosarcomas (19), adamantinomas (4), hemangiosarcomas (9), malignant mixed mammary tumors (5), or perianal adenocarcinomas (7) were accessioned into the study. Out of the total of 236 animals, 9 were lost to follow up. One hundred twenty were treated with radiotherapy alone, and 116 were treated with the combined therapy. Because of the stratification scheme, each of the histological strata was evenly divided between the 2 treatment arms. Tumor volumes were also evenly distributed between the 2 treatment arms, even though tumor volume was not a stratification variable.

Response Rates. The variables of tumor histology, site, volume, heat treatment method, number of heat treatments, and thermal gradient descriptors (Table 1) were examined for their influence on complete response rate. Tumor histology was not an important variable for prediction of CR rate, which confirmed our prior observation (11). Tumor volume was strongly correlated with CR rate when both treatment arms were combined and in each arm separately (Table 3). For both therapy arms, the CR rate tended to drop with increasing tumor volume. The CR rate of tumors treated with radiation alone was more sensitive to increasing tumor volume, however. Tumor volume was also a significant predictor of CR rate when it was examined as a continuous variable in a logistic regression model (\( p < 0.000 \)).

The CR rates for dermal tumors (56%) tended to be higher than for p.o. (49%) or s.c. sites (34%), but the observed differences were not significant in either treatment arm (\( p > 0.05 \)).

Heat treatment had a strong influence on CR rate, with 500-KHz high-frequency heated tumors having a significantly higher CR rate (35 of 47; 74%) than tumors treated with either microwaves (27 of 59; 46%; \( p = 0.003 \)) or XRT alone (38 of 110; 34.5%; \( p < 0.001 \)). The CR rate of microwave-heated tumors was not significantly greater than the XRT alone-treated controls (\( p = 0.153 \)).

Several of the thermal gradient descriptors were significantly correlated with CR rate. For all minima examined, the CR rate tended to increase as the gradient minimum increased. Conversely, the CR rate was inversely related to the value of gradient maxima.

The number of heat fractions received did not influence CR rates, beyond what would be expected for heat + XRT versus XRT alone. The CR rate for animals receiving XRT alone (0 heat fractions) was 36%. For animals receiving 1, 2, 3, and 4 fractions, the CR rate was 67, 79, 45, and 58%, respectively.

Multivariate Analysis. Logistic regression models were used to examine which variables might predict CR rates. The variables which entered the models included tumor volume, heat method, and non-site-specific average minimum (Table 4). The same 3 variables entered the model whether it included all animals or just those who received heat + XRT. For animals receiving XRT alone, tumor volume was the only variable which contributed toward prediction of CR rate. In spite of the highly significant \( p \) values for these variables, the goodness of fit for the models was poor, indicating that not all of the variability was being explained by just those factors. All of the minima shown in Table 5 were correlated with CR rate, with the non-site-specific average minimum being slightly better than the others. Once it entered the model, the other minima did not contribute anything further. When the minima were transformed by taking their natural log, the \( p \) values were lower and goodness of fit was better.

Duration of Response. Direct comparison of duration of response between the 2 treatment arms showed a nonsignificant improvement with adjuvant heat. Several late failures in the heat + XRT group were of particular concern, since they indicated for the overall group, at least, that the percentage of long-term
control was no better for adjuvant heat than it was for XRT alone (Chart 2).

Proportional hazards models were used to investigate which of the prognostic factors were acting independently to affect response duration. By these analyses, it was possible to find specific subgroups which showed significant improvements in response with the adjuvant therapy. For the overall population, tumor histology had a significant influence on duration of response, with mast cell sarcomas showing the longest, and fibrosarcomas the shortest durations of response. Therefore, in each of the models, stratification was by histology. The 2 models examined were: (a) all animals, where animals receiving XRT alone were coded as having no thermal dose; and (b) animals that were randomized to receive heat + XRT. The variables which were considered in the models included tumor site (dermal, p.o., and s.c.), volume (continuous variable), number of heat treatments received, heat treatment method (500 KHz high frequency or 2450 MHz microwave), and the non-site-specific average minimum (continuous variable). In both models, tumor site, number of heat treatments, and heat treatment method were not significant covariates. Tumor volumes and non-site-specific average minimum Eq43 were significant, however.

When all animals were considered, tumor volume alone and non-site-specific average minimum were individually significantly correlated with response (p = 0.0007 and 0.0461, respectively). When both variables were considered, tumor volume entered the model, with p = 0.001, while the thermal dose parameter entered with p = 0.061. Even though this p value was marginally significant, thermal dose was left in the model due to its strong correlation in a 2-way analysis with response duration. When heat + XRT-only animals were considered, tumor volume and non-site-specific average minimum again entered the model (individually, p = 0.025 and 0.021, respectively; together, p = 0.0421 and 0.031, respectively). The influence of these 2 variables on duration of response is shown in Chart 3.

All histological subgroups showed the same heat dose response trends as did the overall population, with the exception of melanomas. As reported earlier, heated and irradiated canine melanomas had a shorter response duration than those receiving XRT alone (11). In this analysis, the same finding was noted and the minimum Eq43 had no influence on response. Squamous cell carcinomas in contrast, had a strong heat-dose relationship (Chart 4).

Normal Tissue Effects

Thermal Injury. The most frequently encountered thermal injury was the skin infarct. This side effect occurred in 45% of all animals in which intact skin was in the heated field. The lesions were known not to be direct full-thickness burns because: (a) surface temperatures were carefully monitored and did not exceed 42.5°C; and (b) they were not detectable immediately after

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**Table 4**

Summary of logistic regression analysis for prediction of CR rates

<table>
<thead>
<tr>
<th>Entered model</th>
<th>Did not enter model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>No. of subjects</td>
</tr>
<tr>
<td>XRT only</td>
<td>110</td>
</tr>
<tr>
<td>Heat + XRT only</td>
<td>108</td>
</tr>
<tr>
<td>XRT and heat + XRT</td>
<td>217</td>
</tr>
</tbody>
</table>

*a NS, not significant.

---

**Table 5**

Influence of thermal gradient minima and maxima on CR rate

<table>
<thead>
<tr>
<th>Minimum first heat treatment</th>
<th>Minimum second heat treatment</th>
<th>Non-site-specific av. minimum</th>
<th>Non-site-specific av. maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose range Eq43</td>
<td>No. of CRs(^2)/no. of animals</td>
<td>Dose range Eq43</td>
<td>No. of CRs(^2)/no. of animals</td>
</tr>
<tr>
<td>XRT alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>36/110 (34.5)%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Heat + XRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11/30 (37)</td>
<td>9/29 (31)</td>
<td>1.0</td>
</tr>
<tr>
<td>1-2</td>
<td>12/19 (63)</td>
<td>15/24 (67)</td>
<td>1.5</td>
</tr>
<tr>
<td>3-15</td>
<td>12/20 (60)</td>
<td>15/60 (25.2)</td>
<td>5.0</td>
</tr>
<tr>
<td>16-40</td>
<td>15/21 (67)</td>
<td>18/22 (62)</td>
<td>10.0</td>
</tr>
<tr>
<td>&gt;40</td>
<td>13/17 (76)</td>
<td>&gt;50</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

\(p = 0.044\) by \(x^2\) test.  
\(p = 0.009\) by \(x^2\) test.  
\(p = 0.006\) by \(x^2\) test.  
\(p = 0.019\) by \(x^2\) test.  
Numbers in parentheses, percentage.
heating. Latent periods of 3 days to 2 weeks were seen between the heat treatment and development of these lesions. During the latent period, the skin was clinically normal. The lesions first became apparent as an erythematous ring surrounding a section of skin, which would first lose tone and blanch, turning yellow. Slowly, over a period of several days, the lesion would dehydrate, turning brown to black. At this point, the lesion could be debrided. We treated the lesions conservatively, relying on granulation processes for healing. Very often the underlying tumor was also necrotic and required debridement. Medical management included routine debridements, flushing with betadine, topical application of sulfadiazine ointments, and parenteral antibiotics.

Full-thickness burns occurred less frequently than did infarcts (10 to 12% incidence). These could be distinguished from infarcts because they were detectable immediately after heating. They were accompanied initially by extensive induration and skin blanching which rapidly progressed to tissue liquefaction within 2 to 3 days. These injuries were managed similarly to the infarcts. Since the animals were anesthetized during treatment, it was not known if some areas of skin were getting too hot. Very often burns resulted from unusual power deposition patterns which were not predicted in advance.

In most cases, both types of thermal injury healed. The time for healing was quite prolonged, however, due to latent XRT effects on the proliferating cutaneous tissues. Many of the lesions persisted up to 2 to 3 months posttreatment, but most (>80%) were healed by 6 months.

In 13.8% of all cases heated, the thermal damage was considered to be unacceptable. Three animals died as a direct result of thermal injury, complicated with tumor bed infections. In 12 cases, the animals developed severe complications which included loss of limb (4), extensive reconstructive surgery (2), loss of eye (2), bacterial spinal meningitis (1), and persistent nonhealing ulcers (3). The incidence of direct thermal injury was not predicted by intratumoral thermal gradient minima. The incidence of skin infarcts did go up as a function of intratumoral gradient maxima, however (Table 6). The gradient maxima also tended to be high in those animals that had unacceptable complications. Four of those animals had doses higher than 900 Eq43, and 11 of 16 were greater than 150 Eq43.

XRT Injury. The overall incidence of moist desquamation was...
not higher in the group of animals receiving the combined therapy (37.9%) than those receiving XRT alone (34.5%). In addition, no thermal dose-response relationship was noted (Table 6).

Examination of all heated animals showed a significantly higher frequency of fibrosis (50%) than was observed in animals receiving XRT alone (34.5%). In addition, no thermal dose-response relationship was noted (Table 6).

Table 6. Relationship of thermal and XRT injury to intratumoral thermal gradients for animals receiving heat + XRT.

<table>
<thead>
<tr>
<th>Injury Description</th>
<th>XRT alone</th>
<th>Heat + XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin irritant</td>
<td>Acceptable</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Unacceptable thermal injury</td>
<td>9/20 (45%)</td>
<td>9/20 (45%)</td>
</tr>
<tr>
<td>Most common post therapy</td>
<td>3/20 (15%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Most common complications</td>
<td>1/20 (5%)</td>
<td>1/20 (5%)</td>
</tr>
</tbody>
</table>

A vs. B | .001 | .004
B vs. C | .012 |
B vs. D | .001 |

Wks, weeks.
M. W. Dewhirst and D. A. Sim

The base of the tongue. observed 8 months posttherapy in a cat with a fibrosarcoma of therapy. This infection may have been the result of thermistor placements in that area. True “late” mandibular necrosis was giving an incidence of 3.6%. The total number of animals evaluable for this late effect was 28, development of fibrosis showed no thermal dose-response relationship, however, and occurred during therapy. One case developed statistically significant.

Bone necrosis was observed in both treatment arms. Four cases were seen in the heat + XRT group. The frequency was 16.7%. Two of those cases were related to direct thermal injury, however, and occurred during therapy. One case developed from a chronic osteomyelitis which occurred 4 months posttherapy. This infection may have been the result of thermistor placements in that area. True “late” mandibular necrosis was observed 8 months posttherapy in a cat with a fibrosarcoma of the base of the tongue.

In the XRT-alone group, mandibular necrosis was seen in one dog 12 months posttherapy for an oral squamous cell carcinoma. The total number of animals evaluable for this late effect was 28, giving an incidence of 3.6%.

Discussion

Tumor Response. The current results of this trial confirm our earlier report that intratumoral thermal gradient minima exert a strong influence on both initial complete response and response duration (10, 11). Similar results have been reported from human Phase I and II trials (23). The early results from our trial and human data indicated that the gradient minimum on the first heat treatment was a better predictor of response than was a site-specific minimum which was averaged over all 4 heat treatments, or an overall average of all sites over all heat treatments. This finding raised concern over the importance of the first treatment in determining the ultimate response of the tumor. In the current analysis, gradient minima from any single heat treatment were similar in their prognostic importance. The best gradient descriptor, however, was the non-site-specific average minimum (the average of the minima from each heat treatment). In addition, since the number of heat treatments received had little influence on tumor response, it can be concluded that the first heat treatment is not singularly important for determination of tumor response.

As noted previously, tumor volume is an important predictor of both initial and long-term tumor response (10, 23). The tumor volume effect is more pronounced for those animals receiving XRT alone than those receiving heat + XRT, but in both cases, the CR rate and duration of response tend to decrease with increasing tumor volume.

The logistic regression models indicated that tumor volume, gradient minimum, and heat methods were strongly correlated with complete response. In spite of this finding, the goodness of fit of the models was poor. This can be interpreted as meaning that other, as yet undefined, variables are also important for prediction of CR rate. Some examples of other potentially important variables might include intratumoral pH and pO2 growth fraction, and vascular physiological and anatomic integrity. Even though we measured as many temperatures as possible, the actual sample sizes were small. In addition, temperature measurement artifact was a potential problem, especially in microwave treatments. It is probable therefore that the actual temperature minima were not measured. It is possible that the goodness of fit may improve with improved thermometry, including methods to improve knowledge of temperature distributions and the use of noninteractive thermometers.

Volume of Tumor Heated. In this study, the tumor temperature minimum continues to be a strong predictor of response. In all our tumors, care was taken to avoid the tumor-normal tissue interface where sharp thermal gradients are known to exist. In addition, only a few positions were monitored. It is unlikely therefore that the actual tumor temperature minimum was always measured. It seems reasonable to assume that the actual percentage of tumor which is heated may be a more important determinant of response than is the absolute minimum. For example, it is possible to envision 2 tumors, both of which have a minimum temperature of 39°C. In one tumor, the minimum represents 1% of the total volume, while in the second tumor it represents 70% of the volume. In this situation, one might expect that the chances of the first tumor achieving a good response would be better than those of the second tumor.

We have begun to look at this volume concept by examining whether none, some, or all of the monitored positions of a tumor are above a certain threshold of Eq 43. We have correlated this with response by looking at TRRs and RRRs. Both statistics have been described in detail previously (11). Briefly, the TRR is the ratio of probabilities of obtaining a CR for heat + XRT versus XRT alone. The RRR describes the relative differences in response duration for the 2 treatment arms. The ratios have been set up so that in both cases a number greater than 1 indicates therapeutic benefit for heat + XRT over XRT alone. The value of the number is an estimate of the strength of the effect. In this analysis, only a few animals fell into the “none” category, and statistical meaning could not be derived from them. Hence, we have examined the thermal dose relationship for “some” versus “all” of the tumor being above 5, 10, 20, 30, 35, and 40 Eq 43 compared to XRT alone. These results show some striking differences in the thermal dose response relationships of response rates and response duration (Chart 5).

For response rates, it is evident that even a small minimum Eq 43 duration (5 min) will increase CR rates by over 2-fold compared with XRT alone. Further increases in minimum Eq 43 min at 43°C gradually increase the TRR further to a maximum of 2.5 for 40 Eq 43. Since the CR rate for radiation alone is 34.5%, a TRR of 2.5 would increase the CR rate to 86.2%. A smaller but significant improvement in CR rate is seen even when only some of the tumor goes above 10 Eq 43 (TRR ~1.5). These results might explain why many investigators have achieved high initial CR rates even when temperatures were not well-documented, and the duration of heating varied.

A more serious concern, however, relates to the dose response relationship for response duration. In this case, it can be seen that getting some of the tumor hot does little toward improving duration of response. In addition, even when all of the tumor is heated, the dose response relationship is more gradual,
reaching a peak value of 2.0 at 30 Eq43. In order to achieve significant improvement in duration of response, more than a minimum of 5 Eq43 will be necessary.

**Normal Tissue Responses versus Issue of Therapeutic Gain.** The classic method for determination of therapeutic gain involves a comparison of the radiation normal-tissue effect dose-response relationship with and without hyperthermia [see Gillette (15)]. One problem with that type of approach is the lack of a way to handle the complications which arise as a result of direct thermal injury to tissues.

In this study, little or no enhancement of early or late XRT effects has been seen. In the case of late fibrosis, the incidence was 1.7 times higher in the heat + XRT group. However, once the animals with burns and infarcts were factored out, the incidence fell to 34.0%, which was not significantly greater than XRT alone. Some fibrosis will occur secondary to granulation healing of an open wound. Therefore, fibrosis in those animals could not be attributed entirely to radiotherapy-induced fibrosis.

Even though the enhancement of XRT effects appears to be minimal, the incidence of serious thermal injury is unacceptably high and detracts from the potential therapeutic gain of this modality. Fortunately, in this study, the incidence of skin infarcts seems to be positively correlated with maximum intratumoral temperature. A similar relationship has been observed in human studies (20). Hence, a way of approaching minimization of this problem may be emerging. Since tumor response is inversely correlated with maximum intratumoral temperature, there is no rationale for pushing to high maxima, especially if critical normal tissues are contiguous with the heated field. This information, together with what was demonstrated for gradient minima, leads one to the conclusion that further research should be directed toward improvements in intratumoral temperature uniformity. A reduction in temperature maxima will reduce the risk of thermal injury, while an increase in temperature minima will increase the likelihood of improved tumor response. In this study, an average minimum of 30 Eq43 would ensure TRRs and RRRs in the plateau range of 2.0 to 2.5 (Chart 5), while an average maximum of 150 Eq43 will keep the incidence of infarcts at less than 5% (Table 6). A fairly small thermal gradient would be necessary to fulfill these requirements. For example, for 30, 60, and 90 min of heating, the temperature minima and maxima would have to be between 43.0° and 45.3°, 42.5° and 44.3°, and 42.2° and 43.7°, respectively.

In summary, the results of this study demonstrate that the heat enhancement of tumor response to heat + XRT is temperature dependent and that a therapeutic gain is achievable with heat + XRT versus XRT alone. Caution should be exercised in extending intratumoral temperatures upwards, since the degree of thermal damage appears to be a function of intratumoral thermal gradient maxima.

**References**

The Utility of Thermal Dose as a Predictor of Tumor and Normal Tissue Responses to Combined Radiation and Hyperthermia

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