Importance of Minimum Tumor Temperature in Determining Early and Long-Term Responses of Spontaneous Canine and Feline Tumors to Heat and Radiation

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ABSTRACT

A total of 130 dogs and cats with squamous cell carcinomas, melanomas, fibrosarcomas, mammary adenocarcinomas, or mast cell sarcomas were randomized to receive radiation (XRT) or heat plus XRT. Time-temperature data for each monitored tumor location were converted to degree-minutes or equivalent min at 43°C (Eq43).

Response rates and durations of response were compared for subgroups of histology, volume, site, and heat treatment method. Thermal gradients existed in all heated tumors. The influence of these gradients on tumor response was examined by correlation of response with degree-minutes and Eq43 minima, maxima, averages, and ranges. A pattern emerged from these analyses linking dose minima, maxima, and ranges with prognostic subgroups as classified by volume, site, or treatment method.

The data indicated that the coolest part of the tumor governed the biological response to combined heat + XRT. Tumors which received a minimum of 35 Eq43 had significantly longer durations of response than did those receiving XRT alone or <3 Eq43 (p < 0.006 and 0.014, respectively; log-rank test). Furthermore, response duration for the combined therapy was significantly longer than heat alone (8, 9) or XRT alone (11).

In spite of these favorable initial results, the question of how to best use heat clinically remains unanswered. The relationship of tumor temperature and duration of heating to clinical outcome remains virtually unexplored. The lack of data in this area is partially due to a lack of noninvasive thermal measurement techniques. Many clinicians have been reluctant to place more than 1 or 2 invasive temperature probes into heated tumors. Hence, very little thermometry data have been accrued.

In clinically heated tumors, temperatures are generally nonuniform with thermal gradients of ±1 to ±2°C or greater, depending on the treatment technique (9, 21, 22). The nonuniform heating leads to different regions of tumor having vastly different thermal histories. In this situation, which part of the tumor governs the biological response? To investigate this question, we undertook a systematic approach to tumor temperature measurement in a randomized trial of spontaneous pet animal cancers treated with XRT alone or heat + XRT. The purpose of this report is to demonstrate the relationship between measured tumor temperature inhomogeneity and treatment outcome, as evaluated by response rates and response duration.

INTRODUCTION

A steadily increasing number of papers are being published on the clinical use of hyperthermia, either by itself or in combination with XRT. Hyperthermia alone has usually yielded only a small fraction of complete responses, and the durations of response have been short (8, 9, 19–23). However, when heat has been combined with XRT, favorable initial results have been obtained, even with low total doses of XRT (15, 19, 21, 27, 33). Comparisons of heat alone and XRT alone versus heat + XRT in patients with multiple skin nodules have demonstrated higher response rates and durations of response in the heat + XRT groups (1, 17, 19). We have reported previously in a prospective randomized trial of pet animal tumors that heat alone and XRT alone had significantly lower CR rates than did the combined therapy (9). Nonresponse rates were significantly higher in animals treated with heat alone than with XRT alone or the combined therapy. Furthermore, response duration for the combined therapy was significantly longer than heat alone (8, 9) or XRT alone (11).

MATERIALS AND METHODS

Animal Patient Population. Pet animals with spontaneous cancer were referred to our clinic by practicing veterinarians in Arizona. The animals either had had no prior treatment, were postsurgical recurrences, or had histologically proven residual disease following surgical excision. The minimum data base on all animals included a history and physical examination, complete blood count, serum chemistry profile, radiographs of the chest and primary tumor site, and an incisional biopsy. Tumor staging was done using guidelines published by WHO (35). Tumor volumes were calculated from the product of 3 orthogonal diameters. The criteria for acceptance into the trial included no evidence of distant metastases, lack of serious concomitant health problems leading to a poor anesthetic risk or less than 1 year of life expectancy, and a tumor site which was felt to be potentially heatable.

The animals were stratified by histological type and randomized to receive radiation alone or a combination of heat and radiation. The heat prescription was 44 ± 2°C for 30 min once/week. The prescribed radiation dose was 460 rads/fraction twice weekly for 8 fractions. When heat was given, it preceded radiation by no more than 10 min.

Treatment Methods. All animals were anesthetized for treatment. They were preanesthetized with atropine sulfate (0.05 mg/kg), induced with thiopental sodium (10 to 20 mg/kg) intubated and maintained on Halothane. Small cats and dogs were masked down with halothane.

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: XRT, radiation; CR, complete response; degree-min, time-temperature integral above 38°C; Eq43, equivalent min at 43°C; Trr, thermal relative rise; RRR, relative reponse rate.

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Most radiation treatments were given using linear accelerators (Varian Associates Clinac 18 or Clinac 4) with X-ray beam energies of 10 or 4 MeV and electron energies of 6, 9, 12, 15, and 18 MeV. In some cases, orthovoltage X-rays were used with energies varying from 60 to 300 kVp (Siemens Stabilopan). Since we encountered such a wide range of patient sizes, we adopted an approach to therapy in which standardized anatomical zones surrounding any tumor were irradiated. A detailed description of this approach has been published previously (9). For example, tumors of the base of the tongue and mandibular gingiva were treated in a field which extended posteriorly from the tip of the mandible to the vertical ramus. A parallel opposed beam of either 10 or 4 MeV X-rays with bilateral bolus was used. Isodose plots were made from contours, and an isodose line was chosen such that the entire anatomical zone, including the tumor, received the minimum prescribed dose. Using this technique, the radiation dose was uniform to 15% within the treated volume. Regional nodes with or without evidence of tumor involvement were treated to the same prescribed dose.

Heat treatments were given using 500-kHz high-frequency current or 2450-MHz microwaves. The high-frequency current technique, which has been fully described elsewhere, utilizes 500 kHz radiofrequency currents passing directly through the heated volume to produce hyperthermia (4, 9, 12). Tissue temperature is controlled by varying power either by the operator or by a thermistor (Yellow Springs Instruments, Model 524) implanted in the tumor and connected to the power generator by means of a feedback loop. Tissue coupling is achieved either by means of copper plates covered with electroconductive jelly on the skin or with rows of serially connected needles placed in the tissue to cover the tumor and a normal tissue margin. The 500-kHz generators included an instrument built by the Los Alamos Scientific Laboratory MP-3 group and an electrosurgical unit (3M Model ESU 500). A 2450-MHz Microwave generator (Hodgway Industries) was also used in some cases. A variety of waveguide applicators were used, depending on the size and location of the tumor.

Thermometry. Intratumor temperatures were monitored using calibrated 26-gauge needle thermistors (Yellow Springs Instruments, Model 524) (3). Between 3 and 8 thermistors were placed in a repeatable geometric array in the heated volume at right angles to the electric field. In the case of 500-kHz heating, power-down measurements were taken to check for artifact. If no artifact was noted, measurements were made with power on. For microwave treatments, temperature measurements were made with power off. Initially, temperatures were manually converted from resistance measurements of the thermistors using digital multimeters. More recently, the procedure has been automated using a microcomputer-controlled sampling system. Temperature measurements were taken at least every 5 min throughout the heat treatment. Detailed measurements of the location of each thermistor within the heated volume were made, including distances from edge of applicators, tumor borders, and other thermistors. When possible, the thermistors were placed back in the same location for each treatment. For each heat treatment, a family of time-temperature curves was obtained which clustered around the prescription of 44° (Chart 1).

The time-temperature data were converted to 2 more convenient forms for analysis. First, the time-temperature integral above 38° was calculated for each tumor location as degree-min. The integral was calculated as follows:

\[
\text{Degree-min} = \int_{0}^{t} (T - 38) \, dt
\]

where \( dt = 5 \) min.

Secondly, the same information was converted to Eq43 by the method of Laprato (30), which utilizes the Arrhenius relationship for biological isoeffect between different time-temperature combinations. The relationship is described by

\[
\text{Eq43} = \sum (d\Delta T) R^{(42.5 - \Delta T)}
\]

where \( d\Delta T = 5 \) min and \( R = 0.25 \) when \( T \leq 42.5° \) and 0.5 when \( T > 42.5° \).

We will hereafter refer to these 2 measures (degree-min and Eq43) as "heat dose," but this does not imply that we believe they are the best way to quantitate thermal dose, nor should they be used that way on a routine clinical basis. The 2 heat dose parameters were calculated for each tumor location (Chart 1, Table 1). For each parameter, we examined the minimum on the first heat treatment, the minimum location averaged over all heat treatments, the average of all locations for all heat treatments, the maximum location averaged over all heat treatments, and the range of all monitored locations for their relationship with tumor response rate and duration of response.

Response End Points. Followup examinations were done at our institution at monthly intervals after completion of therapy. Responses of 1 month's duration or more were categorized as follows: (a) CR = complete regression of all clinical disease; (b) partial response = at least 50% reduction in tumor volume; and (c) no response = less than 50% volume reduction or continued growth. A recurrence was defined as an increase in tumor volume of at least 25% over the smallest posttreatment volume reduction or continued growth. Stable partial responses of 1 year's duration or more were incisionally biopsied. If there was no evidence of disease, they were changed to a CR.

Statistical Methods. Analysis of variance (31) was used to test for differences in the dose parameters between groups (e.g., between

Chart 1. Example. Time-temperature data for one heat treatment of a carpal fibrosarcoma. Seven intratumor positions were monitored, with the minimum temperature being \(-40°\) and the maximum \(-45°\). The same anatomical locations were monitored for all 4 heat treatments. The time-temperature data were condensed to degree-min and Eq43 as described in the text.

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histology or volume groups). Initial response (CR rate) was examined for each variable separately with x-square tests (31). Multivariate analysis for CR rates was done using a logistic regression model as described by Cox (5). The method models the logit of the CR rate \( \ln[p/(1 - p)] \) 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 (28) and Wilcoxon (2, 13) analyses. Both methods test for differences in response duration (time until tumor regrowth) using all the information available, including that in the censored or disease-free animals.

Multivariate analysis of response duration was done using a proportional hazards regression model (6). This technique models the effect of a covariate or risk factor as being multiplicative on the hazard- or time-dependent failure rate.

For both initial and long-term responses, the multivariate analyses allow for interpretation of the relative effects of each of the risk factors. The \( p \) values quoted test for the predictive power of each specific covariate when the other covariates are already in the equation. The descriptive statistics quantitating the strength of the relationship between covariates and outcome were the TRR for initial response and RRR for response duration. The use of these statistics has been fully described elsewhere (11). Briefly, the TRR is the ratio of CR rates for heat + XRT to that for XRT alone. The RRR is the ratio of observed/expected recurrences for XRT alone divided by the same ratio for heart + XRT. For both statistics, a value greater than 1 indicates therapeutic benefit for adjuvant heat. The multivariate models also allow for calculation of equivalent statistics, which take into account the other covariables of the model. Although the statistics are model dependent, they allow for useful data interpretation.

**RESULTS**

**Animal Patient Population**

A total of 89 dogs and 41 cats with either mast cell sarcomas (31), mammary adenocarcinomas (15), squamous cell carcinomas (50), melanomas (18), or fibrosarcomas (16) were accessioned into the study. The numbers receiving XRT alone and heat plus XRT were 69 and 61, respectively. Although stratification was by histology and not by volume, a relatively even distribution of tumor volumes within each histology was observed (Table 2).

**Response Rates**

Histology, volume, site, heating technique, and the thermal dose parameters were examined for their relationship with early CR rates. The fraction of CRs for heat + XRT varied from a minimum of 43% for fibrosarcomas to a maximum of 100% for melanomas. When compared to the corresponding XRT alone group, the ratio of CRs gave TRRs varying from 1.29 for fibrosarcomas to 8.00 for melanomas. All TRRs were greater than 1, suggesting that the addition of heat to XRT increased the CR rate, but the magnitude of the effect was not statistically different between histological groups.

Similarly, the CR rates in both treatment arms depended upon tumor volume. The lowest CR rate was observed in the >100-cu cm group for both treatment arms. The CR rate was strongly dependent on volume in the XRT alone group, dropping steadily from a maximum of 64% for tumors <2 cu cm to 0% for tumors >100 cu cm. The CR rate for heat + XRT was less dependent on volume, and the \( \chi^2 \) test for overall difference in CR rates was not significant. When the 2 extreme volume groups (<2 cu cm versus >100 cu cm) were compared, however, their CR rates were significantly different (0.025 < \( p < 0.05 \) (Table 3).

Tumor site did not seem to affect the CR rate in the heat + XRT group, but it did show an influence on CR rates for XRT alone, with a maximum of 52% for dermal tumors and a minimum of 10% for s.c. tumors (Table 4).

Heat treatment method strongly affected the CR rate. No significant improvement over XRT alone was seen with microwave-heated tumors (32 and 33%, respectively). In contrast, the CR rate for radiofrequency-heated tumors (83%) was greater than either \( \mu \) wave heated tumors or XRT-alone tumors (\( \chi^2 = 14.05, p < 0.005 \) (Table 5).

The relationship between the thermal dose parameters and CR rates was examined by comparing the CR rates for the lowest, 2 intermediate, and highest quartiles of the range observed for each parameter. We assumed that a "good" heat dose description would have an increasing CR rate when one compared the lower versus the higher quartiles. Of the parameters examined, minimum degree-min and minimum Eq43 showed the clearest trend. The trend was more pronounced for the values obtained on the first treatment than the average minimum values obtained from the lowest mean of all heat treatments (Chart 2).

### Table 1

<table>
<thead>
<tr>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Treatment 3</th>
<th>Treatment 4</th>
<th>Avg.</th>
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<tbody>
<tr>
<td>Thermistor no.</td>
<td>Degr-min Eq43</td>
<td>Degr-min Eq43</td>
<td>Degr-min Eq43</td>
<td>Degr-min Eq43</td>
</tr>
<tr>
<td>1</td>
<td>91.2</td>
<td>4.8</td>
<td>117.0</td>
<td>9.9</td>
</tr>
<tr>
<td>2</td>
<td>99.6</td>
<td>6.5</td>
<td>197.2</td>
<td>70.1</td>
</tr>
<tr>
<td>3</td>
<td>150.5</td>
<td>45.1</td>
<td>68.5</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>171.0</td>
<td>60.6</td>
<td>180.0</td>
<td>33.1</td>
</tr>
<tr>
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<td>186.2</td>
<td>82.3</td>
<td>209.5</td>
<td>84.7</td>
</tr>
<tr>
<td>6</td>
<td>135.2</td>
<td>26.3</td>
<td>172.5</td>
<td>46.2</td>
</tr>
<tr>
<td>7</td>
<td>64.2</td>
<td>1.1</td>
<td>50.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Treatment 1 data were extracted from Chart 1 as described in the text.
* This location had the highest average values of degree-min and Eq43 for all 4 treatments.
* This tumor location had the lowest values of degree-min and Eq43 on the first heat treatment and the lowest average value when averaged over all 4 heats.
parameters and heating technique) had an effect on response rates. We questioned whether the difference by biological factors was because the biological aspects limited the dose deliverable to the tumor (as best we could measure it), or whether they were acting independently to affect outcome. To answer this question, we first investigated whether the dose parameters varied by histology, volume, site, or heat technique.

Using analysis of variance, we found that there were few significant differences in the means of any of the heat dose parameters by histology. However, the fibrosarcomas, which had the lowest CR rate (43%), had the highest mean range for both degree-min and equivalent min (p = 0.0126). This was due to both a lower minimum and a higher maximum than those of the other histology groups, although these differences were not individually statistically significant. CR rates for other histologies varied from 57% for mammary adenocarcinomas to 100% for melanomas.

When the mean heat dose parameters were compared by tumor volume groups, the ranges were again statistically different (p = 0.05 for degree-min and 0.008 for Eq43). The broadest ranges were seen in the largest (>100 cu cm) and medium (20 to 50 cu cm) volume groups. These corresponded to the lowest
CR rates (Table 3). The minimum values achieved at first treatment groups (Table 4) were very similar (means of 78.8 and 75.2 degree-min, respectively), whereas the CR rates were different for these 2 groups showing relatively high ranges, low minimums, and high maximums (Table 3).

Tumor site also seemed to influence response duration, with dermal tumors having the largest RRR of 3.13 and oral tumors the low of 0.60. Comparison of thermal dose parameters showed higher maximums and ranges for oral than for dermal tumors. The relationship between measured thermal dose and prognosis for response duration was less clear for oral and s.c. tumors because both had similar heating patterns, yet the RRRs were quite different, being 0.6 and 1.93, respectively (Table 4).

Multivariate Analyses

Logistic Regression Model for Prediction of CR Rates. We used this model to predict CR rates in all animals. The minimum doses delivered on first treatment, whether degree-min or Eq43, were predictive of CR rates. These were coded as 0 = XRT alone and 1, 2, and 3 for the lowest, middle, and highest thirds, respectively. Other variables considered in the model were heating method, tumor volume, histology, and site (Table 6). Method, volume, minimum Eq43 first heat, and site all significantly predicted CR rate, with p < 0.04. Histology had no further predictive advantage for heat.

When only heat + XRT animals were considered, the important variables were method, volume, and histology (p < 0.015). Site and minimum Eq43 first heat could not significantly add to the model (p > 0.43). The significance of minimum Eq43 first heat improvement in response duration (0.15 < p < 0.2, log-rank test) for heat + XRT versus XRT alone. RRRs were used to quantitatively describe the magnitude of the therapeutic benefit of adjuvant heat for different subgroups. The RRRs varied from a low of 0.39 for melanomas (indicating possible therapeutic disadvantage for heat) to a maximum of 7.82 for mammary adenocarcinomas.

The RRRs also varied by tumor volume, going from a minimum of 0.97 for volumes of 20 to 50 cu cm to 2.16 for tumors >100 cu cm. It is of interest to note that the heat dose parameters for these 2 groups showed significantly different RRRs. For oral and s.c. tumors, the RRRs were quite different, being 0.6 and 1.93, respectively (Table 4).

For each of the 8 “thermal dose” parameters, response duration was compared for 4 groups, XRT alone and the groups of animals receiving the lowest, medium, and highest thirds of the distribution for each heat dose parameter. The minimum dose achieved on the first treatment, whether described by degree-min or Eq43, showed significantly improved response duration for the highest heat dose group as compared with XRT alone or the lowest heat group. In contrast, both the overall average and average maximum values were inversely related to long-term response, that is, the longest response durations were observed in the animals in the lowest one-third of the dose distribution. Similarly, the longest response duration was observed in the group of animals with the smallest heat dose range. The minimum Eq43 on the first treatment and the average maximum Eq43 are shown as examples of these trends (Charts 3 and 4). The degree-min parameters showed very similar trends (data not shown).
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Chart 3. Response duration as a function of minimum value obtained on the first heat treatment. The response duration increased significantly when ≥35 Eq43 (d) was obtained compared with no heat [XRT alone (a)] or ≤3 Eq43 (b). Tumors with intermediate heat dose values [4 to 34 Eq43 (c)] fell between the 2 extremes.

Chart 4. Response duration as a function of average maximum monitored thermal dose. A significant difference in response duration was observed between tumors in the lowest one-third of the range [≤70 Eq43 (b)] and XRT alone (a). Conversely, no improvement in response relative to XRT alone was seen for tumors with the highest maximum heat dose values (>134 Eq43 (d)]. This descriptor of thermal dose was inversely related to response.

Table 6

Summary of multivariate analyses/response rates and response durations

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>All animals</td>
<td>124&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Method</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>0.000</td>
</tr>
<tr>
<td>Minimum Eq43 first heat</td>
<td>0.023</td>
</tr>
<tr>
<td>Site</td>
<td>0.039</td>
</tr>
<tr>
<td>Not in model</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>0.2807</td>
</tr>
<tr>
<td>Heat + XRT only</td>
<td>59&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>0.000</td>
</tr>
<tr>
<td>Volume</td>
<td>0.002</td>
</tr>
<tr>
<td>Minimum Eq43 first heat</td>
<td>0.015</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Heat + XRT only</td>
<td>61</td>
</tr>
<tr>
<td>Model</td>
<td></td>
</tr>
<tr>
<td>Minimum Eq43 first heat</td>
<td>0.0362</td>
</tr>
<tr>
<td>Site</td>
<td>0.0262</td>
</tr>
<tr>
<td>Not in model</td>
<td></td>
</tr>
<tr>
<td>Method</td>
<td>0.2102</td>
</tr>
<tr>
<td>Volume</td>
<td>0.4874</td>
</tr>
<tr>
<td>a Logistic regression model.</td>
<td></td>
</tr>
<tr>
<td>b Six animals had microscopic disease.</td>
<td></td>
</tr>
<tr>
<td>c Two animals had microscopic disease.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Table 6 presents the results of multivariate analysis using Cox's regression model to investigate the effects of various prognostic factors on response duration. The model included factors such as initial response rate, method, volume, site, and technique. The statistical significance of each factor is indicated by the p-values, with values less than 0.05 considered significant.

Independent to affect response duration. The statistical technique models the effect of prognostic factors as multiplicative on the hazard rate or rate of recurrence which can vary over time. The effect of treatment was modeled by assuming a base-line hazard for XRT alone. The recurrence rate for heat + XRT equals this base line multiplied by a constant which was estimated from the data. The type of technique is sensitive to low numbers of recurrences, however. We attempted to alleviate the problem by coding the covariates of interest into as few categories as possible, so that the number of recurrences would be sufficient in each group (Table 6).

All heat dose parameters were coded as 0 (XRT alone) or 1, 2, or 3, corresponding to the lower, middle, and upper thirds of each dose group range. The average minimum values had p = 0.1352 and 0.1278 for degree-min and Eq43 when tested individually for prediction of long-term response. However, the same 2 parameters, when measured on the first treatment day only, were significantly correlated with long-term responses (p = 0.0388 and 0.0199 for degree-min and Eq43, respectively).

The other covariates of volume, site, and technique were considered also. Volume aided in prediction of long-term responses, while heating technique and site were not of significant predictive value (p = 0.11 and 0.16, respectively). Therefore, the best model for prediction of response duration, for all animals, was minimum Eq43 on the first treatment and tumor volume (p = 0.0195 and 0.0464, respectively). Histology was used as a stratum variable.

Analysis of the heat + XRT group, without the XRT-alone
animals, still showed minimum Eq43 on the first treatment as being important for prediction of response duration \((p = 0.0362)\). Tumor volume and heating technique were not important \((p = 0.4223 \text{ and } 0.2424, \text{ respectively})\). Tumor site, however, became important \((p = 0.0262)\). Therefore, the best model for predicting response duration for tumors receiving heat + XRT included minimum Eq43 first heat and tumor site. Stratification was by histology.

**DISCUSSION**

Because so many interrelated prognostic variables have been examined in this study, caution should be used, so as not to overinterpret the data. Nevertheless, a consistent pattern seems to be emerging which strongly implicates minimum tumor temperature as the major prognostic factor governing tumor responses to heat + XRT when the radiation dose is fixed: (a) the CR rate was shown to consistently increase when going from the lowest to highest quartiles of the ranges of either degree-min or Eq43 for the average minimum or minimums on first treatment. In contrast, no relationship between CR rate and quartiles was seen for the overall average of all sites or average maximum degree-min or Eq43; (b) a clear relationship between response duration and minimum heat dose was seen (Chart 3).

Examination of overall averages or average maximums and ranges showed an inverse relationship with duration of response. This indicates, for this study, that heating uniformity can influence prognosis. The clinical/biological explanation of this phenomenon is that wider ranges are associated with hot spots, which limit applied power and prevent adequate heating of other parts of tumor. This finding does not imply that non-power-limiting hot spots, as might be observed in a necrotic tumor core, are a poor prognostic sign. (c) for the biological variables examined (histology, volume, site), lower response rates and durations of response in specified subgroups were accompanied by wider dose ranges which were the result of lower minimums and higher maximums. Finally, comparison of the 2 heating techniques again showed a strong correlation between minimum dose and response (Table 5).

The multivariate analyses for response rates demonstrated that the best predictor of early responses was technique, which was indirectly related to temperature, since significantly lower minimums were observed in microwave than in radiofrequency heated animals. Although technique appeared to be a slightly better predictor of early response than did minimum heat dose, there is not an implication that there are nonthermal effects of microwave versus high-frequency heating. Other factors, such as temperature measurement artifact from self-heating of thermistors, rate of heating, or technical biases, may be involved. Further analysis is being done to elucidate this question.

The minimum dose achieved on the first heat treatment was the strongest predictor of long-term responses to the combined treatment (Table 6, Chart 3). Both multivariate analyses demonstrated that the biological parameters of site, volume, and histology could be important and contributed prognostic information which was independent of thermal dose or treatment method.

The strength of the relative therapeutic advantages of the lower, middle, and upper thirds of the heat dose range for minimum Eq43 first heat versus alone was determined from the proportional hazards model. The model predicted a 25% decrease in recurrence rate when going from XRT alone to the lowest third or from the lowest third to the middle third, etc.

We also used the fitted proportional hazards model to calculate estimated RRRs for XRT alone and the lowest, middle,! and upper thirds of heat dose, respectively. This approach to the model allowed us to take into account the effects of tumor volume and site, as well as dose, but assumed linearity for increasing dose. The predicted RRRs for the lowest, middle, and upper thirds of the heat dose range were 1.31, 1.71, and 2.24, respectively. These statistics may be interpreted as meaning that the recurrence rate for the lowest heat dose group \((<3 \text{ Eq43})\) decreased slightly, by a factor of 1.31, over that for XRT alone. Furthermore, the RRR for the high-dose group \((>35 \text{ Eq43})\) was 2.24, indicating over a 2-fold decrease in recurrence rate as compared to radiation alone.

There is strong biological rationale for wanting to quantitate thermal dose. Many in vitro and in vivo studies in tumor and normal tissues have demonstrated that both heat killing and heat radiosensitization are strongly dependent on the absolute temperature as well as the time at a fixed temperature \((7, 16, 24, 26, 29, 32)\). For example, Overgaard (25) has demonstrated for single doses of heat + XRT that the therapeutic gain factor can increase over 2-fold when going from 41.5 to 43.5°C for 1 hr when heat follows XRT by 2 to 3 hrs. In addition, temperature nonuniformity has been correlated with nonuniform biological responses in rodent normal and tumor tissues \((14, 16, 34)\).

In this report, we have shown, in a spontaneous tumor model, that both early and long-term tumor responses are strongly dependent upon minimum monitored tumor temperature and that tumor temperature inhomogeneity will affect responses to heat + XRT. The influence of heating patterns on normal tissue response will be addressed in future papers.

It was not the purpose of this report to purport the use of either degree-min or Eq43 as being the only scientifically valid measurements of thermal dose. They were, however, convenient methods for summarizing a large amount of time-temperature data. A more useful ultimate descriptor might be to quantitate dose in terms of absorbed energy per unit of volume as is currently done with radiation. This type of measure could then be modified to account for biological differences related to thermotolerance, sequencing, variable interfraction intervals, etc.

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**Effects of Temperature on Tumor Response**
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Importance of Minimum Tumor Temperature in Determining Early and Long-Term Responses of Spontaneous Canine and Feline Tumors to Heat and Radiation

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