Correlation between Initial and Long-Term Responses of Spontaneous Pet Animal Tumors to Heat and Radiation or Radiation Alone

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ABSTRACT
Most early-phase testing of new therapeutic modalities involves analysis of initial tumor response as opposed to estimation of long-term response. In this study, the validity of initial response rates to predict long-term responses was examined for tumors treated with radiotherapy alone compared with heat combined with radiotherapy.

A total of 130 pet animals with either squamous cell carcinomas, melanomas, fibrosarcomas, mammary adenocarcinomas, or mast cell sarcomas were randomized to receive either radiation alone (XRT) or heat + radiation (A + XRT). Responses to treatment were evaluated by response rates and response duration.

The complete response (CR) rates were consistently higher for A + XRT than for XRT across different histology groups. The combined therapy led to prolonged tumor response in all histological subgroups except melanomas, which had a longer response duration when treated with XRT alone (p = 0.043). This was in spite of a relatively high CR rate in that group (100% versus 12.5% for A + XRT and XRT, respectively). In contrast, while no significant improvement in CR rate was observed for dermal squamous cell carcinomas treated with A + XRT (XRT = 52.9%; A + XRT = 68.8%), a significant improvement in response duration was noted (p = 0.002). These are two examples where CR rate did not predict long-term response.

When all histological subgroups were combined (except melanomas), the CR rate was higher (p < 0.001), and response duration was prolonged (p = 0.031) for A + XRT compared to XRT alone.

INTRODUCTION
High initial response rates have been reported in many human Phase I and II trials for hyperthermia combined with XRT (A + XRT). The data have been particularly encouraging for those tumors which are known to be relatively radioresistant, such as sarcomas, melanomas, adenocarcinomas, and large locally advanced tumors of a variety of histological types (1, 10–13). The XRT doses used have been quite modest, with the response rates and durations of response for the combination therapy being higher than those for radiotherapy alone in those groups of patients where multiple lesions were treated (1, 11, 12). Because follow-up times have been short, however, little information has been available on the usefulness of heat toward increasing the fraction of long-term responses over that of radiotherapy alone.

A Phase III trial has enabled us to evaluate initial and long-term responses for XRT alone versus A + XRT for pet animals with a variety of spontaneous tumor histologies, sites, and volumes. Some of the results of this ongoing trial will be presented. The emphasis will be to demonstrate how initial response rates do not reliably predict long-term responses.

MATERIALS AND METHODS
Animals were referred to our clinic by practicing veterinarians in Arizona. These animals either had no prior treatment or were postsurgical recurrences. The minimum data base on all patients included a history and physical examination, complete blood count, serum chemistry profile, radiographs of the chest and primary tumor site (when necessary), and an incisional biopsy.

Histopathology. Biopsy specimens were submitted for histopathology. In some cases, fresh frozen sections were cut, stained with a rapid hematoxylin-eosin stain, and read for an immediate diagnosis prior to treatment. In all cases, however, tissue was fixed in 10% buffered formalin for processing of paraffin sections. Paraffin blocks were subsequently sectioned, stained with hematoxylin-eosin, and read by light microscopy. Special stains were used on the tumors to aid in tumor-type classification.

Tumor diagnosis was made on the basis of recognition of morphological characteristics accepted for each tumor type. Tumors were classified as benign or malignant, and malignant tumors were further described as to degree of anaplasia, mitotic index, necrosis, and local invasion. If a diagnosis could not be made from available tissue, a request for rebiopsy was made. In cases which were not readily identified as to tumor type, at least 3 pathologists reviewed the slides to determine a morphological diagnosis. Recurrences of tumors were also evaluated histologically to reconfirm original diagnosis, and to identify changes in individual tumor morphology.

Staging of tumors was done using guidelines published by WHO (21). Tumor volumes were calculated from the product of 3 orthogonal diameters. Animals were accepted into the trial if the tumor was malignant, if there was no evidence of distant disease, and if the tumor was accessible for heating.

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

Treatment Methods. The details of the heating and radiotherapy techniques have been published elsewhere (5, 6). Briefly, the heat treatments were given with 500-KHz high-frequency current with direct or capacitive coupling to the tissue or with 2450-MHz μ-waves. Intratumor temperatures were monitored by placement of between 3 and seven 26-gauge needle thermistor probes (Yellow Springs Instruments) within the tumor. They were placed in a repeatable geometric array so that the same regions of tumor could be monitored on successive heating. In the case of 500-KHz high-frequency heating, the thermistor probes were placed at right angles to the electric field to minimize perturbation and heating.
artifact. Measurements were taken with power on and off to check for artifact. With 2450-MHz $\mu$-waves, measurements were taken with power off. Temperatures were recorded at least every 5 min throughout the heat treatment. Typically, a family of heating curves would be obtained which clustered around the temperature prescription of 44°.

For most tumors, the time to steady state was less than 5 min. The heat treatment began when steady state was achieved and continued for 30 min from that point. Ideally, steady state was defined as that point where all monitored locations were between 42 and 46°. As will be discussed later, it was not always possible to achieve that goal because of hot spots which were near critical normal tissues, such as overlying skin, teeth or bone. When overheating of normal tissues did not occur, we sometimes allowed tumor temperature maxima to exceed 46° to bring the minimum monitored point above 42°. Cool-down kinetics were not measured because of the short time requirement between cessation of heating and XRT (less than 10 min) (Chart 1).

The XRT treatments were given with either 10-MeV X-rays; 6-, 9-, 12-, 15-, or 18-MeV electrons, or orthovoltage X-rays. Standardized radiation fields were designed to encompass the tumor volume plus a large normal tissue margin. This was done to ensure that the tumor radiation doses were equivalent in both treatment arms. The details of this approach have been published previously (5). For example, tumors of the mandibular gingiva, floor of mouth, and base of tongue were treated in a field which extended posteriorly from the tip of the mandible to the wing of the atlas. A parallel opposed beam of 10-MeV X-rays was used with 2-cm bolus on both sides. Isodose plots were made from contours, and the appropriate isodose line was chosen so that the minimum tumor dose was that prescribed.

Follow-up examinations were done at our institution at monthly intervals after completion of therapy. Responses of 1-month duration or more were categorized as follows: (a) CR, complete regression of all clinical disease; (b) PR, at least 50% reduction in tumor volume; (c) NR, less than 50% volume reduction or continued growth; and (d) a recurrence, which was defined as an increase in tumor volume of at least 25% over the smallest posttreatment volume or the reappearance of primary tumor following CR. Suspected recurrences were verified by biopsy.

Methods of Analysis. Two different parameters were used to measure "heat dose" achieved in the tumor. The time-temperature integral above 38° was calculated for each tumor location and averaged over all treatments to give degree-minutes at each location. Minimum and maximum degree-minutes, corresponding to "dose" achieved at the coolest and hottest monitored portions of the tumor, were explored in terms of correlation with outcome. We also converted the data to equivalent minutes at 43° by the method of Sapareto (18). Again, these measures were averaged over all treatments for each location, and the minimum and maximum were considered.

Initial responses were described by response rates and TRRs (ratios of probabilities of obtaining a CR for $\Delta$ + XRT versus XRT alone). Length of response was described by time until disease progression. Differences in response duration were evaluated by logrank and Wilcoxon statistics (16, 17). RRRs (relative ratios of observed versus expected number of subjects with disease progression) were used to describe the relative differences in response duration for different subgroups (2, 3). For TRRs and RRRs, a number greater than one indicated therapeutic benefit of $\Delta$ + XRT over XRT alone. Direct comparison of TRRs and RRRs gave an estimate of the relative strength of the therapeutic benefit when evaluated by initial CR and response duration, respectively. If the treatment effect on response rates was predictive of the same effect on response duration, one would expect the TRRs and RRRs to be similar in magnitude. Please refer to "Appendix" for detailed description of TTR and RRR. Comparisons of mean values of heat dose parameters were made with "t" statistics (19).
Initial and Long-Term Tumor Response

Table 1  
| Volume distribution by histology for Δ + XRT and XRT alone |
|---|---|---|---|---|---|
| <2 cm | 2 to 20 cm | 20 to 50 cm | 50 to 100 cm | >100 cm |
| Δ + XRT | XRT | Δ + XRT | XRT | Δ + XRT | XRT |
| Mast cell sarcoma | 4 | 3 | 7 | 5 | 0 | 4 | 2 | 1 | 2 | 3 |
| Mammary adenocarcinoma | 1 | 0 | 2 | 4 | 1 | 0 | 3 | 0 | 2 | 15 |
| Melanoma | 3 | 4 | 3 | 2 | 0 | 1 | 2 | 1 | 0 | 2 | 18 |
| Fibrosarcoma | 2 | 1 | 0 | 2 | 2 | 0 | 3 | 4 | 1 | 16 |
| Squamous cell carcinoma | 10 | 10 | 7 | 9 | 4 | 3 | 3 | 0 | 1 | 50 |
| Total | 30 | 30 | 20 | 20 | 10 | 10 | 10 | 10 | 10 | 10 |

Table 2  
Comparison of response rates by histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of animals</th>
<th>Complete (%)</th>
<th>Partial (%)</th>
<th>None (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell sarcoma</td>
<td>XRT</td>
<td>(15)</td>
<td>5 (33)</td>
<td>6 (40)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(13)</td>
<td>10 (77)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>XRT</td>
<td>(8)</td>
<td>1 (12)</td>
<td>5 (62)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(8)</td>
<td>6 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mammary adenocarcinoma</td>
<td>XRT</td>
<td>(8)</td>
<td>1 (12)</td>
<td>5 (62)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(7)</td>
<td>4 (57)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>XRT</td>
<td>(9)</td>
<td>3 (33)</td>
<td>5 (56)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(7)</td>
<td>3 (43)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>XRT</td>
<td>(25)</td>
<td>11 (44)</td>
<td>7 (28)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(24)</td>
<td>15 (62)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Total</td>
<td>XRT</td>
<td>(65)</td>
<td>21 (32)</td>
<td>28 (43)</td>
</tr>
<tr>
<td></td>
<td>Δ + XRT</td>
<td>(59)</td>
<td>40 (68)</td>
<td>14 (24)</td>
</tr>
</tbody>
</table>

Number in parentheses, number of subjects in each category.

Table 3  
Comparison of strengths of initial response differential (TRR) and response duration differential (RRR) by histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>TRR</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell sarcoma</td>
<td>2.31</td>
<td>1.23</td>
</tr>
<tr>
<td>Mammary adenocarcinoma</td>
<td>4.57</td>
<td>7.82</td>
</tr>
<tr>
<td>Melanoma</td>
<td>8.00</td>
<td>0.29</td>
</tr>
<tr>
<td>Overall without melanoma</td>
<td>1.79</td>
<td>1.85</td>
</tr>
<tr>
<td>Overall with melanoma</td>
<td>2.10</td>
<td>1.41</td>
</tr>
</tbody>
</table>

Numbers in parentheses, number of subjects in each category.

Numbers >1 indicate a greater effect for Δ + XRT than for XRT alone.  
Significantly higher CR rate for Δ + XRT than for XRT alone (p < 0.001).

the histology groups. However, a decreased NR rate was not seen with fibrosarcomas. The most striking pattern was seen in the melanomas, where only one CR was seen in the XRT alone group (1 of 8), whereas all responses in the Δ + XRT group were complete (8 of 8). Even though the number of animals in this group was relatively small, a significantly higher CR rate for Δ + XRT was observed for melanomas (corrected χ², p = 0.005; Fisher’s exact test, p = 0.006). The CR rates seemed to vary by histological subgroup. However, these differences were not significant (Cochran’s test for homogeneity, 0.05 < p < 0.1). The difference in CR rate for the whole population yielded a significant improvement with adjuvant heat (68%) compared with XRT alone (32%) (stratified χ², p < 0.001) (19).

The statistic which describes the magnitude of the therapeutic benefit for adjuvant heat in terms of initial response is the TRR, which compares the CR rate for Δ + XRT to that of XRT alone (Table 3). The TRRs varied in magnitude, from a high of 8.0 for melanomas to a low of 1.29 for fibrosarcomas. For TRRs, a number greater than one indicated therapeutic benefit for adjuvant heat. The magnitude of the statistic gives a qualitative estimate of the strength of the effect.

Comparison of response duration for the 2 treatments was made using stratified logrank methods. This allowed for variation in relapse rates with XRT alone for histological subgroups. This analysis yielded a nonsignificant improvement in response duration for adjuvant heat (logrank = 1.78; 0.15 < p < 0.2). An examination of histological subgroups was made to see if any showed a tendency toward a therapeutic disadvantage for adjuvant heat. This was done by examining response duration curves and RRR values. With the exception of melanomas, all histologies had RRRs greater than one, indicating longer response duration with adjuvant heat. The difference in response duration was statistically significant for mammary adenocarcinomas (logrank p = 0.03) (Table 3). In the case of melanomas, the RRR was 0.29, suggesting a shorter response duration for adjuvant heat. This observation was corroborated by formal analysis of response duration curves (logrank p = 0.042) (Chart 2). When melanomas were removed from the overall population, a significant improvement in response duration for adjuvant heat was observed (logrank = 4.66; p = 0.03) (Chart 3). Clearly, the removal of melanomas from the population affected the outcome of the response duration analysis.

The reason for the aberrant response of melanomas might have been related to either an inherent resistance to combined heat and XRT or to other interrelated prognostic factors. The difference could not be explained by tumor volume, since no obvious skewing in the distribution was observed for melanomas compared with other histologies (Table 1). The difference might have been related to tumor site, however, since 6 of 8 heated melanomas were in the oral cavity.

Because of the technical difficulties involved in heating oral tumors, our clinical impression was that we were not heating them very well. We explored this hypothesis by examining a second histological subgroup, squamous cell carcinomas. These tumors occurred in 2 sites, oral and dermal. The thermal dose parameters for oral and dermal sites were compared. The values for minimum heat dose were higher for dermal than oral sites (but not significantly so), while values of maximum heat dose were significantly lower (p = 0.05). These data suggested that less uniform heating was being achieved with oral than with
dermal tumors. When the dose ranges and variances were compared, they confirmed the impression. Similar trends were observed for oral squamous cell carcinomas and melanomas (Tables 4 and 5). Hence, the relationship between the observed thermal dose patterns and response of squamous cell carcinomas was made by comparing the 2 sites. No improvement in CR rate was seen for either site when comparing $\Delta + \text{XRT}$ to XRT (Table 4). Response duration for the 2 treatments was no differ-

tent for oral tumors, but was significantly greater for $\Delta + \text{XRT}$ than for XRT alone for dermal tumors (logrank, 9.502; $p = 0.002$; Wilcoxon, 2.65; $p = 0.008$) (Chart 4). Furthermore, a comparison between oral and dermal tumors which received $\Delta + \text{XRT}$ showed significantly improved response duration in the latter (logrank, $p = 0.007$; Wilcoxon, $p = 0.007$). The same comparison for tumors receiving XRT alone revealed no significant difference in response duration.

Since XRT alone yielded no difference in response duration for the 2 sites, the variation observed for $\Delta + \text{XRT}$ could not be attributed to inherent differences in radiosensitivity. In addition, tumor volumes did not differ significantly for the 2 sites. Therefore, it seemed reasonable to assume that the site differences in $\Delta + \text{XRT}$ response duration could be strongly related to differences in heating patterns. Since melanomas had similar heating patterns, it is possible that their lack of long-term response was due to inadequate heating. It remains to be determined whether improved duration of response could be obtained when adequate heating is achieved in melanomas.

The difference in heating patterns for oral and dermal tumors is visually demonstrated in Chart 5 for 2 typical cases. In both cases, 500-KHz high frequency current heating was used. In the

### Table 4

<table>
<thead>
<tr>
<th>Site and species</th>
<th>Mean volume (cm$^3$)</th>
<th>CR rate (%)</th>
<th>TRR</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cat XRT</td>
<td>21.1</td>
<td>2/4 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta + \text{XRT}$</td>
<td>17.0</td>
<td>2/3 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog XRT</td>
<td>34.2</td>
<td>1/4 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta + \text{XRT}$</td>
<td>23.9</td>
<td>1/3 (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total XRT</td>
<td>3/8 (37.5)</td>
<td>3/6 (50.0)</td>
<td>1.33</td>
<td>0.549</td>
</tr>
<tr>
<td>Dermal Cat XRT</td>
<td>2.5</td>
<td>7/12 (58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta + \text{XRT}$</td>
<td>1.8</td>
<td>6/11 (54.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog XRT</td>
<td>28.1</td>
<td>2/5 (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta + \text{XRT}$</td>
<td>33.3</td>
<td>5/5 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total XRT</td>
<td>9/17 (52.9)</td>
<td>11/16 (68.8)</td>
<td>1.38</td>
<td>7.26</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Dose parameter</th>
<th>Squamous cell carcinoma$^a$ (mean of 16 dermal subjects)</th>
<th>Squamous cell carcinoma (mean of 6 oral subjects)</th>
<th>Melanoma (mean of 6 oral subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum degree-minutes</td>
<td>$142.9 \pm 49.8^b$</td>
<td>$126.3 \pm 70.3$</td>
<td>$157.2 \pm 21.0$</td>
</tr>
<tr>
<td>Maximum degree-minutes</td>
<td>$196.6 \pm 26.1$</td>
<td>$230.3 \pm 59.1$</td>
<td>$221.8^c \pm 54.0$</td>
</tr>
<tr>
<td>Minimum equivalent minutes $^c$</td>
<td>$37.9 \pm 24.0$</td>
<td>$30.8 \pm 32.4$</td>
<td>$51.0 \pm 27.4$</td>
</tr>
<tr>
<td>Maximum equivalent minutes $^c$</td>
<td>$96.6 \pm 61.9$</td>
<td>$462.5^c \pm 807.2$</td>
<td>$244.5^c \pm 281.1$</td>
</tr>
</tbody>
</table>

$^a$ Range of measured degree-minutes was significantly higher in the oral than the dermal squamous cell carcinomas ($p = 0.043$).

$^b$ Mean ± S.D.

$^c$ Significantly higher than same parameter for dermal squamous cell carcinomas ($p < 0.05$).
Initial and Long-Term Tumor Response

Chart 4. Response duration of squamous cell carcinomas by site. The response duration of oral tumors was not improved over XRT alone when heat was added. (Curve A versus Curve B; logrank = 0.675; p = 0.411; Wilcoxon = -0.84; p = 0.396). In contrast, a highly significant improvement in response duration was noted when heat was added to XRT in dermal tumors (Curve C versus Curve D; logrank = 9.5; p = 0.002; Wilcoxon = 2.65; p = 0.008). Comparison of response durations for heated tumors by site showed longer responses in dermal than in oral tumors (Curve B versus Curve C; logrank and Wilcoxon, p = 0.007). The same site comparison for tumors receiving XRT alone revealed no difference in response duration (Curve A versus Curve D). A: oral heat + XRT; total, 6; fail, 4. O: oral XRT; total, 8; fail, 3. A: dermal heat + XRT; total, 16; fail, 2. •: dermal XRT; total, 17; fail, 10.

dermal tumor, relatively uniform heating was obtained because of easy access and no interference with vital structures. The oral tumor, on the other hand, was growing on both sides of the dental arcade and the lip. A hot spot developed during the treatment which required a reduction in applied power. This resulted in an inadequate temperature distribution with some areas of tumor never reaching therapeutic levels. The same type of heating pattern was often observed in melanomas, which were predominantly oral as well (Table 6).

DISCUSSION

Malignant Melanomas. Much of the current enthusiasm over the potential of hyperthermia as an adjuvant to radiation has been generated because of the high initial response rates which have been obtained in tumor histologies which are known to be relatively radioresistant. The most striking results have been with malignant melanomas, where CR rates have been greater than 90% (11-13). In this study, the CR rate was 100% for melanomas, indicating similarity between the human and canine experiences. However, the most disappointing result of this current study was that most of the melanomas which received Δ + XRT relapsed, and the rate of relapse was shorter than for those tumors which received XRT alone. The obvious conclusion which arose from this observation was that the high initial response was not at all predictive of response duration. The next question which arose was whether a similar experience would occur in human melanomas. Of course, one major difference between human and canine melanomas is site, being dermal and oral for the 2 species, respectively. Hence, the major reason for making the site comparison for squamous cell carcinomas was to determine if the lack of long-term therapeutic benefit could be attributed to poor thermal dose patterns in oral sites. Nonuniform temperatures have been shown to affect both tumor and normal tissue responses to heat (4, 7, 9, 11, 20). This analysis also supported that concept. However, without a significant number

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of canine dermal melanomas, it is not currently possible to examine whether improved thermal dose patterns would lead to improved long-term control for that histology. The mechanism for the high initial response rate is unclear, but may be related to vascular collapse within the tumor bed. Those tumor cells which are deeply infiltrated into adjacent normal tissue and which are (a) not affected by the vascular collapse; and (b) not heated adequately may be responsible for tumor regrowth. Based on this analysis, it is reasonable to conclude that the experience with melanomas in this study may not be predictive of long-term response of human melanomas to Δ + XRT.

Correlation between Early and Long-Term Tumor Response. The major emphasis of this paper has been to compare the incidences of tumor CR rates and response durations. A relatively simple way to make this comparison is through the use of TRRs and RRRs. These descriptive statistics have been discussed in detail in the "Appendix." In this case, both statistics have been derived so that numbers greater than one indicate improvement in response with adjuvant heat.

The size of the statistics relates to the magnitude of the advantage. For example, the TRR for mammary adenocarcinomas was 4.57 (Table 3). This can be interpreted as meaning that a tumor receiving Δ + XRT has a 4.57-fold greater risk (chance) of achieving a CR than if it were treated with XRT alone. Similarly, the RRR of 7.82 means that a tumor has a 7.8-fold greater chance of maintaining heat response than a similar tumor treated with XRT alone that has been followed for the same length of time. The TRRs and RRRs were of similar magnitude for mast cell sarcomas, mammary adenocarcinomas, squamous cell carcinomas, fibrosarcomas, and all histological groups combined (without melanomas). In all of the cases, the values are greater than one, indicating a therapeutic advantage for heat. Formal testing showed the advantage to be significantly different compared to one for mammary adenocarcinomas and the combined population without melanomas. Therefore, in these cases, the initial response rates seemed to be good predictors of long-term response. However, 2 examples were shown which demonstrated a lack of correlation between CR rates and response duration. In one case (malignant melanoma), the Δ + XRT response rate of 100% (TRR = 8.00; Table 4) totally misrepresented the relative duration of response, where Δ + XRT was significantly shorter than XRT alone. On the other extreme, dermal squamous cell carcinomas demonstrated no significant difference in CR rates for the 2 treatments but demonstrated a highly significant improvement in response duration. The results of this study underscore: (a) the inherent dangers involved in analyzing new therapeutic modalities in a setting where only initial tumor response can be evaluated; and (b) the necessity for establishing Phase II testing of Δ + XRT in human patients where the ultimate objective is long-term local control. In some cases, modalities which cannot maintain long-term response may advance to Phase III studies. Conversely, new modalities may be overlooked because the initial responses are no different than controls, whereas they may improve response duration.

Summary. The results of this study were: (a) initial and long-term response of tumors to Δ + XRT were not reliably correlated; and (b) long-term response of squamous cell carcinomas was related to tumor site. Analysis of thermal dose data indicated this difference might be the result of wider dose distributions for oral compared to dermal sites.

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APPENDIX

Statistical Considerations (2, 3)

TRR. The TRR is defined as:

\[
\frac{\% \text{ of } CR \text{ with } Δ + XRT}{\% \text{ of } CR \text{ with } XRT \text{ alone}}
\]

This statistic is commonly used in prospective studies of disease incidence, comparing a group with a risk factor to a group without; hence, the name, "relative risk." If the TRR is greater than unity, a benefit is indicated for the Δ + XRT group, whereas, if the TRR is less than one, more CRs occurred in the XRT-alone group. The question naturally arises: if we observe a TRR greater than one, can we be sure that it indicates a true therapeutic benefit, or could the 2 treatments be equally advantageous with respect to CR rate, and by chance we observed a high TRR? That is, is the TRR statistically different from one? To answer this question, one would use a \( z^2 \) test to see if the 2 CR rates differ (18). Where appropriate, such tests have been performed on the data presented here. Given that a difference is statistically confirmed, the TRR indicates the strength of the difference. If the TRR is 0.3, then a CR occurs only 30% as often with Δ + XRT as it does with XRT alone.

Relationship between the TRR and the Thermal Enhancement Ratio. The thermal enhancement ratio is ascertained for a specified biological isoeffect, e.g., 50% tumor control, by:

\[
\text{Thermal enhancement ratio} = \frac{XRT \text{ dose required to get effect using } Δ + XRT}{XRT \text{ dose required to get effect using } XRT}\]

If adjuvant heat has therapeutic benefit, then the thermal enhancement ratio will be greater than unity. If not, the thermal enhancement ratio will be no more than one. Thermal enhancement ratios can be calculated when several different XRT doses have been used but cannot be calculated when all animals received the same Δ + XRT dose, as was done in this study. The TRR and the thermal enhancement ratio are alike in that values greater than unity denote a therapeutic benefit for adjuvant heat, and values less than one denote a therapeutic disadvantage for adjuvant heat. However, they differ when one attempts to interpret the magnitude of the ratio. A TRR of 3 means that animals who received Δ + XRT are 3 times as likely to achieve a CR than are those receiving XRT alone. A thermal enhancement ratio of 3 means that 3 times the XRT dose is needed for an isoeffect if used alone rather than with heat.

Response Duration Curve Analysis. Because the animals in this study have been followed for different periods of time posttreatment, the Kaplan-Meier or product-limit method of calculating the response duration curve was used. In this method, the fraction of animals without disease progression at a specific time posttreatment is the ratio of those animals who had been followed for that long and had not recurred, divided by the total number of animals that had been followed for that long. Thus, the curve drops at each time when a recurrence is observed. These recurrences are represented by a symbol on the chart. The small vertical bars on the charts reflect time points where an animal was censored, i.e., at least one animal was followed to that time posttreatment without a recurrence.

To compare 2 response duration curves (e.g., to compare the curve for Δ + XRT to that for the XRT alone), 2 statistics are applicable. For both the logrank and Wilcoxon statistics, the expected number of recurrences in each group is
calculated under the null hypothesis assumption that both groups are recurring at an equal rate per week of observation. Therefore, the expected number of recurrences takes into account any difference in follow-up times for the 2 groups. This expected number is then compared to the observed number of recurrences.

The logrank and Wilcoxon statistics, although testing the same hypothesis, do so in different ways. The Wilcoxon statistic weights differences between observed and expected number of recurrences heaviest where there are the most observations, i.e., at early times posttreatment, whereas the logrank places equal emphasis to differences at each time point. Therefore, the Wilcoxon test is more likely to detect differences in the curves at early time points, and the logrank is more likely to detect differences at later follow-up times. Those interested in a further discussion of these techniques should refer to the works of Peto et al. (16, 17), of E. Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52: 203–223, 1965), and of N. Breslow (A generalized Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship, Biometrika, 57: 579–594, 1970).

RRA, in addition to the formal statistical methods used to compare response duration curves, we wanted a descriptive measure of the relative therapeutic benefit of the 2 treatments. We used the ideas of Peto et al. (16, 17), adapted slightly, to calculate a RRR:

For each animal, we recorded the time from end of treatment until recurrence or the last date they were seen and were stable. The number of recurrences observed depended on the number of weeks the animals had been followed: i.e., those who had been followed for only a short period of time did not have as much chance to recur as did those followed for a longer period. Under the null hypothesis of no treatment difference, the recurrence rates are the same for both groups and would differ only if one group had, on the average, longer follow-up than the other. Therefore, the expected number of recurrences is calculated for each treatment group, based on an overall estimated recurrence rate and the observed follow-up times in that group. If one treatment is worse than the other, more occurrences will be observed in that group than were expected, so that the ratio of observed/expected would be greater than one. At the same time, the ratio of observed/expected in the better group will be less than one. Therefore, the ratio:

\[
\text{RRR} = \frac{\text{Observed recurrences with XRT}}{\text{Expected recurrences with XRT}} / \frac{\text{Observed recurrences with A + XRT}}{\text{Expected recurrences with A + XRT}}
\]

will be greater than unity if XRT is the worse treatment and less than one if XRT is worse.

Note on Interpretation

Both the TRR and RRR are valuable tools to describe the strength of treatment differences for initial responses and response durations, respectively. In contrast, formal statistical tests (logrank, Wilcoxon, and \(\chi^2\)) are the proper means to arrive at significance levels. However, once a difference has been found statistically significant, the TRR and RRR can be used to describe the magnitude of the effect, and can suggest new questions to be asked.

REFERENCES


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Correlation between Initial and Long-Term Responses of Spontaneous Pet Animal Tumors to Heat and Radiation or Radiation Alone

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