Irradiation-Hyperthermia in Canine Hemangiopericytomas: Large-Animal Model for Therapeutic Response

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ABSTRACT

Results of irradiation-hyperthermia treatment in 11 dogs with naturally occurring hemangiopericytomas are reported. Similarities of canine and human hemangiopericytomas are described. Orthovoltage X-irradiation followed by microwave-induced hyperthermia resulted in a 91% objective response rate. A statistical procedure was given to evaluate quantitatively the clinical behavior of locally invasive, nonmetastatic tumors in dogs that were undergoing therapy for control of local disease. The procedure used a small sample size and demonstrated distribution of the data on a scaled response as well as transformation of the data through classical parametric and nonparametric statistical methods. These statistical methods set confidence limits on the population mean and placed tolerance limits on a population percentage. Application of the statistical methods to human and animal clinical trials is apparent.

Key words. – cancer, carcinoma, clinical response, lymphoma, sarcoma, small sample size, statistical methods.

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ABBREVIATIONS USED: CGy = centigray; CR = complete remission; kVP = kilovolts peak; P = progression; PCOP = Purdue Comparative Oncology Program; PR = partial remission; R = relapse; SD = stable disease.
Canine hemangiopericytomas are excellent comparative models for human soft-tissue sarcomas. Their behaviors, histopathological appearances, blood supplies, and therapeutic responses are similar to those of human sarcomas (1-13). In dogs hemangiopericytomas are often bulky soft-tissue sarcomas that are encountered on the extremities. They are occasionally seen over the chest wall and neck. Retroperitoneal lesions, frequently encountered in cases of human hemangiopericytoma, are rare in the dog. The tumors become more prevalent with advancing age. Ninety-five percent of the dogs with hemangiopericytomas presented to veterinarians are 6-14 years of age. Radiographs do not demonstrate boney invasion. The blood supply to these neoplasms is usually adequate to maintain tissue viability, even in large tumor masses, but it is typically less than the blood supply of surrounding normal tissues.

The histopathological appearance of canine hemangiopericytomas is like that of modified fibrosarcomas (1-3) and develops in a whorling cellular arrangement, frequently termed a "fingerprint" pattern. The malignant growths seem to originate from the vascular sheath (in humans, called pericytes of Zimmermann) around open or collapsed capillaries. Individual cells of hemangiopericytomas usually contain plump, ovoid nuclei, unlike the more flattened spindle cells of fibrosarcomas and other mesenchymal growths.

Clinically, hemangiopericytomas behave in a locally invasive, nonmetastatic manner and generally do not respond well to any single routine therapy. Their recurrence rates after surgical excision have ranged from 25 to 60%. Tumors with a high mitotic index are more likely to recur (2). Available literature does not show that either irradiation or chemotherapy alone can effectively control hemangiopericytomas.

The present study provides preliminary data on the effects of orthovoltage irradiation in combination with microwave-induced hyperthermia in spontaneous canine hemangiopericytomas. We chose the dog over the rodent as the animal model because 1) the tumor-to-patient size ratio is more comparable to that of humans, 2) it is extremely difficult to administer heat to rodent tumors without creating regional or systemic heating, whereas in the dog heat administration is relatively easily achieved, and 3) heating instruments of the size designed for humans may be used on dogs, whereas they are too large for use in rodents. We chose this particular tumor as a model because 1) it is spontaneously occurring and may therefore resemble human tumors more than induced or transplanted tumors, 2) it lacks systemic involvement, and 3) therapy is easily applied to lesions on extremities or the body wall.

Problems arose in trying to evaluate quantitatively the effectiveness of the treatment. It was difficult to document accurately tumor volume before therapy because of irregular tumor shape and varying degrees of normal tissue infiltration. It was also virtually impossible to measure accurately tumor volume during therapy because of tissue reactions (e.g., ulceration, necrosis, inflammation, and varying surface characteristics). Therefore, to evaluate quantitatively the effectiveness of the treatment, we constructed and evaluated a rating scale to describe the clinical behavior of a locally invasive, nonmetastatic tumor undergoing therapy for control of local disease. The statistical methods used to evaluate the rating scale seem to be unique in comparative oncology: Using a relatively small sample size, we were able to predict with a high degree of confidence that 1) our findings were representative of the population as a whole,
2) tumor response following completion of therapy could be documented objectively, and, 3) our clinical observations were statistically significant. This paper uses these statistical methods to present the results of treatment of canine hemangiopericytomas with both irradiation therapy and hyperthermia.

MATERIALS AND METHODS

Animals.-- Eleven dogs with histopathologically confirmed hemangiopericytomas were procured through the PCOP and presented to the Small Animal Clinic, Purdue University, for pretreatment and post-treatment evaluations. The PCOP is a network of over 140 cooperating veterinarians from Lafayette and Indianapolis, Indiana and is dedicated to the compassionate use of pet animals with spontaneous neoplasia as models for human as well as veterinary cancer therapy. The dogs underwent treatment between July 1980 and February 1983. Laboratory profiles, including a complete hemogram, serum biochemical evaluation, urinalysis, and screening for parasites, were obtained prior to each dog's initial entry into the study. Radiographic evaluations of the thorax, abdomen, and primary lesions were conducted on all animals. The tumors underwent biopsy, and the animals were clinically staged and classified according to standards published by the World Health Organization (14). Dogs with local disease were entered into the study only if they were expected to survive 6 weeks or more. The dogs were maintained in their home environments between treatments and after courses of therapy were completed. Careful follow-up was conducted by direct examination. Final survival dates were verified by telephone contact.

Therapy.-- Chemical restraint was induced following the administration of atropine sulfate (0.05 mg/kg) given sc. Twenty minutes later a mixture of ketamine HCl (2.2 mg/kg) (Ketaset®, Bristol Laboratories Inc., Syracuse, N.Y.) and xylazine (1.1 mg/kg) (Rompun®; Haver-Lockhart, Shawnee, Kansas) was given iv by a bolus over 5 seconds. Repeat administration of the chemical restraint was occasionally required to maintain immobilization during prolonged therapy. Radiation was delivered at 7-day intervals by either a 200- or a 300-kVP orthovoltage X-ray therapy unit with a half-value layer of 1.1 mm Cu or 1.42 mm Cu, respectively. Fractions were delivered in increments of either 400-600 CGy with the 200-kVP unit or 800 CGy with the 300-kVP unit. Immediately after X-ray therapy, the dogs were given local heat therapy with either an Elmed 2,450-MHz diathermy unit or a Burdick 2,450-MHz microwave generator. A 2-cm air gap was maintained between the surface of the microwave applicator and the tumor. Core body temperature was monitored periodically by rectal probes. Invasive needle-mounted thermistors or thermocouples, placed either directly into the tumor or into preplaced Teflon catheters, were used to monitor intratumoral and surrounding temperatures. Periodic monitoring in three to six intratumoral locations was conducted. Hyperthermia was administered for 20-30 minutes, and the animals were allowed to recover. One “course of treatment” was defined as seven weekly treatments or a portion thereof needed to induce CR of the tumor. CR was determined by clinical observation and confirmed by biopsy and histopathological examination of the tumor site. Response to therapy was evaluated immediately following completion of a course of treatment; additional evaluations were made 1 month and 3 months, 6 months, and then every 6 months thereafter. Tumor response was classified as CR, PR, SD, R, or P (table 1).
Statistical methods and analysis.-- In this study survival was important and was evaluated; however, response to local therapy in this non-life-threatening tumor model had equal or greater importance. The goal of our analysis was to measure the animal’s intermediate response to therapy without waiting until death. We adopted a "scaled response" statistical analysis in which numerical scores were assigned to clinical status as follows: P = −2, R = −1, SD = 0, PR = +1, and CR = +2 (table 1). Each dog in the study was assigned a response score, according to this scale, from −2 to +2. Dogs demonstrating initial improvement and then R had their scores summed, thereby providing an overall performance score for that course of therapy (table 2). Such scores were not assigned until 30 days after a course of treatment was completed.

### TABLE I. Response to therapy; Scaled response

<table>
<thead>
<tr>
<th>Response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all clinical evidence of active tumor, +2.</td>
</tr>
<tr>
<td>PR</td>
<td>Decrease of ≥50% in the sum of the products of all diameters (anterior–posterior, ventral–dorsal, and medial–lateral) of measured lesions, +1.</td>
</tr>
<tr>
<td>SD</td>
<td>Steady state or response less than PR or P. There can be neither any appearance of new lesions nor any worsening of symptoms. 0.</td>
</tr>
<tr>
<td>R</td>
<td>A) Appearance of new lesions from CR. B) Reappearance of old lesions in patients who had CR. C) For patients in PR, an increase of ≥50% in the sum of the products of the diameters of all measured tumors over the sum obtained at the time of maximum regression, −1.</td>
</tr>
<tr>
<td>P</td>
<td>Unequivocal increase of at least 50% in the size of any measurable lesion, −2.</td>
</tr>
</tbody>
</table>

The statistical evaluation of the scaled responses assumes that the variable is continuous between the integers and the spacing is truly equal. The key concept of the analysis is to calculate the 95% confidence interval for either the mean response score, when more powerful parametric methods are used, or the median response score, when nonparametric methods are used. If the 95% confidence limits overlap a response score of zero, then the therapy has no significant effect. If the 95% confidence intervals include a range of scores strictly greater than zero, then the therapy does have significant benefit in local palliation. Finally, if the 95% confidence intervals include a range of scores strictly less than zero, the therapy is significantly detrimental to local control.
TABLE 2. Response by course of therapy score

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One course of treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CR</td>
<td>+2</td>
</tr>
<tr>
<td>4</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>5</td>
<td>PR</td>
<td>+1</td>
</tr>
<tr>
<td>6</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>7</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>8</td>
<td>CR</td>
<td>+2</td>
</tr>
<tr>
<td>9</td>
<td>CR</td>
<td>+2</td>
</tr>
<tr>
<td>10</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>11</td>
<td>CR</td>
<td>+2</td>
</tr>
<tr>
<td><strong>Two courses of treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td>7</td>
<td>CR</td>
<td>+2</td>
</tr>
<tr>
<td>10</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
<tr>
<td><strong>Three courses of treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CR, R</td>
<td>(+2, -1)=+1</td>
</tr>
</tbody>
</table>

n=11 dogs

An adequate sample size must be assured to allow the extremes of the sample to be at least the 95% confidence interval on the mean. A minimum of 6 dogs must be used in any such study for parametric evaluation (15). If nonparametric methods are used to establish a 95% confidence interval for the median, the extreme data points are excluded so the second and next-to-last data points would be used. If 7 dogs are evaluated by this method, the first and last data points in the array have to be used, thereby precluding the establishment of a 95% confidence interval. In this study there were 11 dogs. Ideally, at least 12 dogs might have been studied because then the third and the third-to-last point for the interval could have been used, thereby allowing elimination of more than one extreme data point for the nonparametric analysis.
In this study, a decision had to be made whether to use a parametric or a nonparametric analysis of the scaled responses. A parametric analysis was preferable to nonparametric procedures because its confidence and tolerance intervals are shorter. For parametric methods to be used, the population from which the scaled responses come must be approximately normal. Since the sample size is usually less than 50, the Shapiro-Wilk W-test should be used to test for normality (16-20). If the test for normality is accepted, the parametric procedures may be used on the scaled responses. Although the probability, $\beta$, of accepting the hypothesis when it is false may be large, the probability, $\alpha$, of rejecting the hypothesis when it is true may be set at 0.01. A small $\alpha$ is suggested because the t-distribution is to be used to set a confidence interval on the population mean, and the t statistic is quite robust (i.e., allows nearly correct confidence intervals even when the population is not quite normal). If the population is not approximately normal, the data should be transformed and rechecked for normality (16-20).

If the transformed data allow acceptance of a normal distribution, parametric data analysis may still be used and a confidence interval on the transformed population mean may be calculated. The lower and upper limits of this confidence interval are determined, and those limits are retransformed to the original scale. This final confidence interval is not determined by a “least-squares” analysis (the most desirable method of calculating an estimate), but it is routinely used by applied statisticians. In this way, 95% confidence intervals for the mean response scores may be constructed for the subjects studied. If a suitable transformation cannot be found after several tries, a nonparametric median confidence interval may be constructed. This interval will be wider than a parametric mean confidence interval, but it is statistically sound.

In addition to finding the confidence interval on the population mean, many investigators are interested in finding the percent of the population that will lie above the lowest observed response in the experimental group with a certain confidence. This statistic is called a one-sided tolerance limit. In a like manner for the confidence interval on the population mean, the one-sided tolerance limit may be constructed for either the parametric or the nonparametric case.

RESULTS

Clinical Response

An initial objective response rate of 91% was obtained in the 11 dogs studied (table 2). Nine animals demonstrated CR; one PR; and one SD. Of the 9 dogs in CR, five demonstrated R at 60-340 days following CR (table 3), and three were available for a second course of therapy. Of the three dogs treated again, 100% demonstrated CR: One died in CR; two demonstrated R at 46 and 61 days after therapy. Of these two relapsing dogs, one underwent euthanasia with persistent tumor 159 days later. The other received a third course of therapy and underwent CR, but it relapsed 422 days later and was eventually sacrificed. Of the eleven dogs, five either died free of tumor or remained tumor-free.
All eleven cases showed therapeutic complications including ulceration of the tumor site, and most developed tumor necrosis with sloughing and eventual healing by second intention. Two dogs had distant metastases of the tumor. In one case, it was necessary to administer hydralazine according to the method of Voorhees and Babbs (21) to achieve selective heating of the tumor.

TABLE 3. Survival

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Days to R&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Days survived after initial treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>215</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>729</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>520</td>
<td>Underwent euthanasia&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>46</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
<td>422</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>340</td>
<td>687</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>266</td>
<td>71</td>
<td>Underwent euthanasia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>NA</td>
<td>349</td>
<td>Underwent euthanasia&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>NA</td>
<td>&gt;435</td>
<td>Died&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>117</td>
<td>577</td>
<td>Alive&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>NA</td>
<td>&gt;365</td>
<td>Alive&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Date of evaluation, December 31, 1983.  
<sup>b</sup> NA=not applicable.  
<sup>c</sup> Tumor present at treatment site.  
<sup>d</sup> Free of tumor.  
<sup>e</sup> Metastasis.

**Temperatures Achieved**

Intratumoral temperatures of greater than 43 °C for 10 minutes were planned and achieved at least once in all dogs; however, the ease with which we obtained this goal was extremely variable among dogs and also among treatments for the same dog. We found it extremely difficult to heat tumors less than 3 cm<sup>3</sup> to 43 °C without also heating the surrounding tissue to this cytotoxic temperature. Desired temperatures became increasingly difficult or impossible to achieve as tumors ulcerated, sloughed, and decreased in bulk during the courses of therapy. Homogeneous temperature distributions throughout the tumors were difficult to obtain. Heat was deposited most intensely under the center of the microwave applicator, so the heat source had to be moved from point to point over the tumor to obtain total tumor heating. Furthermore, since
microwave heating interfered with accurate thermometry, temperature monitoring was limited to brief, intermittent periods when the microwave generators were turned off. While heat was being applied, the invasive temperature probes were removed from the tumors. Microwave power was turned off every 3-5 minutes while the temperature probes were inserted and moved from site to site within and around the tumor. Approximately 10 seconds was needed at each of the three to six thermometry sites to obtain stable temperature readings; thus the last of six measured sites was not monitored until more than a minute of cooling time had occurred after cessation of microwave power. The tumors seemed to heat in a "stair-step" manner. However, the increments of temperature rise in the early minutes of heating were often small, followed by an unpredictable major temperature elevation to greater than 50 °C. Table 4 summarizes the heat dose obtained during all treatments for each dog.

### TABLE 4. Heat dose

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>No. of treatments</th>
<th>One course of treatment</th>
<th>Two courses of treatment</th>
<th>Three courses of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total min at 43–50°C &gt;50°C &gt;63°C</td>
<td>Highest degree C</td>
<td>Scored response</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>41  8  49</td>
<td>59.7</td>
<td>+1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>31  7  38</td>
<td>54.0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>21  0  21</td>
<td>45.6</td>
<td>+2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>43  26  69</td>
<td>56.1</td>
<td>+1</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>14  5  19</td>
<td>50.8</td>
<td>+1</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>39  27  66</td>
<td>52.4</td>
<td>+1</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>41  7  48</td>
<td>51.2</td>
<td>+1</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>69  27  96</td>
<td>53.3</td>
<td>+2</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>29  15  44</td>
<td>56.6</td>
<td>+2</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>12  0  12</td>
<td>50.0</td>
<td>+1</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>47  0  47</td>
<td>48.0</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>43  7  50</td>
<td>50.8</td>
<td>+1</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>127  21  148</td>
<td>56.0</td>
<td>+2</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>65  0  65</td>
<td>46.1</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>64  36  100</td>
<td>56.0</td>
<td>+1</td>
</tr>
</tbody>
</table>
Statistical Analyses

a) The ordered response scores for the 11 animals were (0, 1, 1, 1, 1, 1, 2, 2, 2, 2, 2). These scaled responses are denoted \( y_i \)  where \( i = 1, 2, \ldots, 11 \) and the sample size is \( n = 11 \).

b) The Shapiro-Wilk W-test for normality yielded \( W = 0.793 \) (see "Appendix A") and was greater than the theoretical \( W \) (0.792) for \( \alpha = 0.01 \). Hence the hypothesis that the data are normally distributed was accepted.

c) The 95% confidence interval on the population mean, \( \mu \), of the scaled response was calculated. It ranged from 0.84 to 1.71 (see "Appendix B"). Since the 95% confidence interval does not include the value zero, significant local palliation was caused by irradiation combined with hyperthermia. If use of \( \alpha = 0.01 \) is considered too liberal, the weaker nonparametric procedure may be used satisfactorily. A 98.8% confidence interval may be established by use of the same array (0, 1, 1, 1, 1, 2, 2, 2, 2) and (15), on the basis of a sample size of 11, where the second and the second-to-last values are the extremes (i.e., 1, 2). Although this example looks very good compared to our parametric evaluation, which gave a 95% confidence interval of 0.84-1.71 assuming normality, this same result for the nonparametric confidence interval should be understood to occur for the array 0, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2.

d) The parametric one-sided (upper) tolerance limit (see "Appendix C") indicated that we could be 90% confident that 89% of the population of dogs treated as we treated these dogs would have an objective clinical improvement (i.e., a scaled response greater than zero). If the one-sided tolerance limit were applied to the nonparametrically evaluated data, a sample size of 11 would allow 70% confidence that 89% of the population would be scored greater than zero (i.e., clinically improved) for a similar population of treated dogs.

DISCUSSION

Of 11 dogs in this study, 10 showed improvement. This objective response rate of 91% suggests that irradiation when combined with hyperthermia is an effective method of treating hemangiopericytomas in dogs. Statistical methods show that this response is quantitatively significant. Not only did our small sample size meet criteria necessary to reflect the population as a whole, but the outcome also predicted with a 90% confidence that the observed responses were beneficial to 89% of the patients. This method of statistical analysis of scored clinical responses in small numbers of patients appears to solve a common problem in clinical research: It provides an objective method to evaluate critically data accumulated under conditions requiring clinical observations where precise measurements are difficult to obtain.

Relapse in 5 cases may have resulted from inadequate X-radiation doses, since therapies were interrupted once CR was obtained (table 5). Biopsy samples taken from ulcerated margins at the time of CR revealed no residual microscopic foci of tumor; however, only a small portion of any tumor site could be sampled, and viable tumor cells were apparently left in situ where they
caused the tumor to relapse. A search of the literature from 1967 to the present reveals only poor response of fibrosarcomas to irradiation therapy (22, 23) and no success in treating canine hemangiopericytomas with irradiation therapy alone. In an attempt to correlate total radiation dose with the scored response, we constructed text-figure 1. The distribution suggested that a total radiation dose of at least 2,000 CGy provided the best response. Our present study suggests that adequate radiation doses combined with hyperthermia may be effective in controlling canine hemangiopericytomas.

TEXT-FIGURE I. Radiation dose vs. scored response (numbers denote dog No.).
Local complications of irradiation-hyperthermia included thermal burns of both normal and neoplastic tissues when temperatures exceeded 45 °C. This result occurred at least once during the course of treatment in all 11 dogs. The burns and tumor necrosis resulted in open wounds and healing by second intention. Other complications included infection of the wounds, moderate anorexia, and fever, all of which were controlled by systemic antibiotic support. Long-term side effects included skin fibrosis, alopecia, and loss of pigmentation of the hair in the treatment field. Mild contracture of underlying tendons was also observed in 1 dog. These side effects were not life threatening. These were the only toxicities observed in the entire study.

Temperature measurements actually may have been underestimated, since the measurement technique utilized intermittent hyperthermia, with temperature measurements recorded up to 1 minute after the microwave source was turned off. However, recent improvements in technology permit simultaneous heating and temperature monitoring so that burns need not develop.

An attempt to correlate total thermal dose (min at > 43 °C), tumor size, and tumor location with the scored responses failed to reveal information that was helpful in predicting response to therapy. Text-figures 2-4 demonstrate these findings. As expected, most of the hemangiopericytomas occurred on the extremities, and there seemed to be no correlation of location with scored responses. Scored responses of +2 occurred in dogs receiving both low and high thermal doses as well as in dogs with both large and small tumors. Although extreme temperature elevations (> 50 °C) can cause thermal burns, and although it might be possible to cause tumor regression by protein coagulation, necrosis, and sloughing; our data did not suggest that such were the case. As many CR's were observed in dogs whose tumors never exceeded 50 °C (dogs #3 and #11) as were observed in those that did reach such tissue-destructive temperatures. Additionally, we used hyperthermia alone in preliminary studies (Richardson RC, Voorhees WD III, Janas W, Babbs CF: Unpublished data) in an attempt to treat four hemangiopericytomas, one fibrosarcoma, one squamous cell carcinoma, and two transmissible venereal tumors in dogs. Temperatures greater than 50 °C were routinely obtained for at least 20 minutes. Ulceration and sloughing occurred, but no significant tumor regression was observed.
TEXT-Figure 2. Thermal dose vs. scored response (numbers denote dog No.).
TEXT-FIGURE 3. Tumor size vs. scored response (numbers denote dog No.).
TEXT-FIGURE 4. Tumor location vs. scored response (numbers denote dog No.).
The unexpected metastasis of 2 hemangiopericytomas in this study might suggest that irradiation-hyperthermia stimulates metastatic events, as has been reported for osteogenic sarcomas (24). Our data, however, do not support this conclusion. One dog (#5) had received one course of irradiation-hyperthermia, resulting in PR. Because tumor growth could not be controlled, the affected leg was amputated. At the time of amputation, no evidence of metastatic tumor was observed. Following amputation, axillary lymph node metastasis was observed and the dog underwent euthanasia. Necropsy revealed numerous pulmonary metastatic nodules. Although irradiation-hyperthermia may have stimulated a shedding of cells and metastasis, it is equally possible that they were present and undetected before treatment began, which would be problematic. The other case (#10) was not aggravated by experimental treatment; it had failed two courses of therapy, and this dog was sacrificed following repeated unsuccessful attempts to control the tumor surgically. Necropsy revealed pulmonary metastasis; however, careful review of radiographs made prior to any treatment demonstrated small pulmonary nodules that had not been observed initially. Metastasis had occurred in this dog before therapy had ever begun, as may well have been the case for dog #5. On the basis of observations of metastasis in cases such as these, until further studies have been conducted, this form of therapy should not be condemned.

The positive response of this naturally occurring canine tumor to irradiation-hyperthermia is encouraging. Credence is provided to this response by statistical methods designed to evaluate a small sample size taken from the population as a whole. The benefits of such therapy should be confirmed in additional spontaneous large-animal models.

APPENDIX A

Shapiro-Wilk W-test for normality:

1) Calculate the sums of squares (SS), standard deviation (s), and the mean (\(\bar{y}\)):

\[
SS = \sum_{i=1}^{11} (y_i - \bar{y})^2 = 4.18
\]

\[
s = \sqrt{\frac{SS}{n-1}} = \sqrt{\frac{4.18}{10}} = \sqrt{0.418} = 0.647
\]

\[
\bar{y} = \frac{\sum y}{n} = \frac{14}{11} = 1.273
\]

2) Calculate \(b\) by subtracting each low score from its corresponding high score in the array of scores [e.g., last high score (2) minus first low score (0), next-to-last high score (2) minus second low score (1), etc.] and by multiplying the result by the appropriate coefficient (16-20):

\(b = 0.5601 \times (2-0) + 0.3315 \times (2-1) + 0.2260 \times (2-1) + 0.1429 \times (2-1) + 0.0695 \times (1-1) = 1.8206.\)
3) Calculate the Shapiro-Wilk W-coefficient:

\[
W = \frac{b^2}{SS} = \frac{(1.8206)^2}{4.18} = 0.793
\]

4) Compare W with the theoretical W (0.792) using \( a = 0.01 \), which is indicated by the “percentage points” (16-20).

5) Since the observed W (0.793) is greater than the theoretical W (0.792), accept the hypothesis that the distribution from which the array 0, 1, 1, 1, 1, 1, 2, 2, 2, 2 came is normal.

APPENDIX B

The 95% confidence interval for the mean:

\[
(\bar{y} - t_{0.025}^{10 df} \bar{s}_y < \mu < \bar{y} + t_{0.025}^{10 df} \bar{s}_y),
\]

where

\[
\bar{y} = \text{the sample mean of the scaled responses}
\]
\[
y = 1.273
\]
\[
t_{10 df}^{0.025} = t_0^Q = \text{the value of } t \text{ (16–20) for } Q = 0.025
\]
and \( df = \text{degrees of freedom} = n - 1 = 10 \)

\[
t_{10 df}^{0.025} = 2.228
\]

\[
s = \text{standard deviation} = \sqrt{0.148} = 0.647
\]

\[
\bar{s}_y = \frac{s}{\sqrt{n}} = \frac{\sqrt{0.418}}{\sqrt{11}} = \text{standard error of mean}
\]

and \( \mu = \text{population mean for which the confidence interval is estimated} \)

\[
[1.273 - (2.228)(0.195) < \mu < 1.273 + (2.228)(0.195)]
\]

or

\[
[0.84 < \mu < 1.71].
\]
APPENDIX C

One-sided tolerance limit: To establish the lower limit of the tolerance interval (\( \bar{y} - K_s \)) as 0, set (\( \bar{y} - K_s \)) = 0; knowing \( \bar{y} = 1.273 \) and \( s = \sqrt{0.418} \) from the data, K turned out to be \( \approx 1.97 \). We utilized the method given in Odeh and Owen (25) to find a value of K that nearly matched the K = 1.97, where GAMMA = the confidence that the proportion is correct = 0.900, \( p = \) proportion of the population greater than the smallest scaled response (0) in the data = 0.900, and \( N = n = 11 \). Since the tabled K = 2.011 is greater than the calculated K = 1.97, we interpolated between 1.219 for 0.750 = \( p \) and 2.011 for 0.900 = \( p \), to obtain a value of approximately 0.89.

REFERENCES


(12) BREDT AB, SERPICK AA. Metastatic hemangiopericytoma treated with vincristine and actinomycin D. Cancer 1969; 24:266-269.


