

Large Animal Studies of Hyperthermia and Irradiation¹

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Abstract

Investigators who have studied hyperthermic response of spontaneous animal tumors have reported complete remission for variable periods of 15 to 38% of tumors treated. Normal tissue complications were minimal. Long-term control appears more likely if irradiation is combined with hyperthermia, but information is lacking to date to confirm this. Dose-response assays of radiation alone have been done which would make comparisons with hyperthermia and radiation more meaningful. Probabilities for increasing tumor control without significantly increasing normal tissue response can be estimated better from such assays. Spontaneous tumors in companion animals have advantages over rodent tumor systems of relatively larger treatment fields; longer follow-up times are possible, and serial monitoring of a variety of clinical data can be done. Experience of investigators using these tumors has shown that animal owners and referring veterinarians are most cooperative in reasonable, humane approaches to experimental cancer therapy.

Spontaneous tumors in domestic animals were used by early radiologists to provide guidelines for radiation therapy in humans (6). Since that early period, spontaneous tumors have been a largely neglected resource for comparative oncology (4). In recent years, canine tumors have been used to evaluate whole-body irradiation for lymphomas (12) and to compare effects of neutrons with γ -radiation prior to clinical trials in humans (1). However, relatively little work has been done either on the design of appropriate therapeutic protocols for treatment of animal tumors or to utilize that information to provide a basis for human cancer therapy. This is due primarily to the expense of facilities and lack of interested and trained personnel.

Veterinary radiation therapy is based largely on the work of Pommer (13). His monograph of treatment of benign and malignant diseases in animals remains the most complete of its type. A few papers on radiation therapy of animals have been published in recent years (7-9, 11, 16, 18).

Investigators interested in the use of hyperthermia in cancer therapy have studied the response of naturally occurring tumors in larger animals (3, 5, 13). Much of the interest in hyperthermia at Colorado State University was inspired by report of Crile (5) in 1962 of a study of 30 spontaneous tumors in dogs. From that time until very recently, little work has been done using tumors in companion animals as experimental models for evaluation of hyperthermia and irradiation.

Irradiation Alone. At Texas A & M University, 210 canine tumors were treated to compare tumor response following X- or γ -irradiation to that following neutron irradiation (1, 2). Doses were given in 8 equal fractions over a 4-week interval. Forty-one % of squamous cell carcinomas were controlled for 2 years

with 4120 rads of X- or γ -rays and 22% were controlled with 1872 rads of neutrons (Table 1). Based on preliminary data, a relative biological effectiveness of 2.2 was chosen at the beginning of the study to establish the neutron doses. Twenty-eight % of the adenocarcinomas were controlled with 4120 rads of X- or γ rays, and none were controlled with 1872 rads of neutrons. The tumors controlled were primarily nasal adenocarcinomas. Thirteen % of mast cell tumors were controlled with either 3656 rads of X- or γ -rays. None were treated with neutrons. Unfortunately, no comment was made on normal tissue response; however, as the dogs with controlled tumors were followed for at least 2 years, the normal tissue complications must have been minimal.

A study was done in 1974-75 at Colorado State University in which 25 dogs with squamous cell carcinomas of the oral cavity were irradiated (10). A ⁶⁰Co teletherapy unit was used. Seventeen of the dogs had tumors of similar size involving the gingival mucosa. A dose-response assay was done by randomizing to variable dose levels. The total dose was given in 10 equal fractions on a Monday-Wednesday-Friday schedule. Follow-up information was obtained for all these dogs at one year. A probit analysis was done to determine the TCD₅₀² (Table 2). The value obtained was 3750 rads with a 95% confidence interval of 3470 to 4050 rads. Although a study was not designed specifically to determine a 50% necrosis dose, sufficient observations were made of dogs given irradiation for head and neck tumors to indicate that the 50% probability for necrosis was 4900 rads with a 95% confidence interval of 4540 to 5290 rads.

A recent analysis of the response of 23 mast cell tumors treated with X- or γ -rays at Colorado State University indicated a TCD₅₀ of 3625 rads with a 95% confidence interval of 3265 to 4025 rads.³

It is difficult to compare the studies from the 2 institutions; however, the TCD₅₀'s obtained in the Colorado State University studies appear somewhat lower than would have been predicted from the Texas study. However, more fractions given in a shorter total time interval may be more effective. The TCD₅₀'s may also have been higher had the analysis been done after a 2-year follow-up as was done in the Texas study.

Hyperthermia Alone. Investigators at the University of Arizona, the University of New Mexico, and Stanford University have studied the response of spontaneous animal tumors to hyperthermia. At the University of Arizona, radio-frequency current field techniques were used to produce localized hyperthermia (14). Twenty-four animals with a variety of tumors were subjected to single or multiple treatments. The aim of the preliminary study was to establish a reasonable dose regimen for testing in a randomized trial. Some of the tumors were very advanced and were not followed sufficiently long for a quali-

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² TCD₅₀, tumor control dose, probability of control of 50% of the tumors.

³ G. S. Allan, and E. L. Gillette. Radiation response of canine mast cell tumors, submitted to the Journal of the National Cancer Institute.

Table 1
Response of canine tumors to X- or γ -rays and neutrons
Based on work of Banks et al. (1, 3).

	X- or γ -rays	No. controlled		
		Dose ^a (rads)	Neutrons	Dose (rads)
Squamous cell carcinomas	9/22 (41) ^b	4120	2/9 (22)	1872
Adenocarcinomas	5/18 (28)	4120	0/4 (0)	1872
Mast cell tumors	2/16 (13)	3656		

^a All doses were given in 8 equal fractions during a 4-week period.

^b Numbers in parentheses, percent controlled.

Table 2
Canine tumor and normal tissue response for tumors treated at
Colorado State University

	TCD ₅₀ (rads)	Viable cell inoculum for 50% tumor takes (rads)
Squamous cell carcinomas	3750 (3470–4050) ^a	4900 (4540–5290)
Mast cell tumors	3625 (3265–4025)	

^a 95% confidence interval.

Table 3
Remission of animal tumors following hyperthermic therapy at three
institutions

	Method	Fraction in complete re- mission	Length of remission
Stanford Uni- versity	43–44.5°C for 30 min; 3–6 treatments; (ultrasound)	3/20	6–64 wk
University of Arizona	44°C for 30 min; 4 treat- ments; (radio-frequency current)	9/24	>6 mos.
University of New Mexico	45°C for 30–40 min; 1–2 treatments; (radio-fre- quency current)	6/16	>10 mos.

tative evaluation of tumor response. However, it was stated that 50% of the tumors treated had marked regression with complete remission for at least 6 months in 9 instances (Table 3). Included in the group of 24 tumors were 7 squamous cell carcinomas of which 2 regressed. A typical hyperthermia treatment was a tumor temperature of 43°C for 30 min. Four such treatments were usually given.

Crile (5) reported that mast cell tumors responded well to hyperthermia. In his study, only the mast cell tumors and lymphomas were controlled with heat alone. Crile used a temperature of 48°C for 75 min in treatment of mast cell tumors.

Day⁴ reported complete regression for greater than 10 months for 6 of 16 tumors treated with localized current field (Table 3). The 6 tumors controlled included 1 squamous cell carcinoma, 3 mast cell tumors, 1 perianal adenoma, and 1 basal cell carcinoma. An intratumor temperature of 45°C was maintained for 30 to 40 min.

Marmor *et al.* (13) recently reported response of tumors of dogs and cats to hyperthermia induced with ultrasound (Table 3). Intratumor temperatures of 43, 44, or 44.5°C were maintained for 30 min. Three to 6 treatments were given each tumor. Twenty animals were treated with tumors less than 2 cm in diameter and less than 3 cm deep. Three squamous cell carcinomas completely regressed from 6 weeks to greater than a year. Some response was seen in other types of tumors

including partial regression of 2 mast cell tumors. They stated that the squamous cell carcinomas appeared to be the most responsive in that 7 of 8 showed some response to hyperthermia. They were particularly impressed by the lack of side effects using ultrasound. Some surface burns were observed at the site of the thermocouple insertion. They stated that ultrasound is an effective and safe method of heating surface tumors and causing regression in some spontaneous tumors. In their study, some surface cooling was obtained by pumping cool water through the face of the transducer.

Hyperthermia and Irradiation. Connor *et al.* (3) recently reported studies of hyperthermia and irradiation of tumors of companion animals. Thirty-five animals were treated with a variety of courses of heat plus radiation. Most tumors were given 4 weekly hyperthermia treatments of 44°C for 30 min and two 500-rad, 4 mV X-ray doses weekly for 4 weeks. The treatment had a positive effect, that is, at least 50% tumor regression in 83% of the animals. More than one-half of the tumors completely regressed. About one-half those that had complete regression, however, had recurrences within 6 months.

Day² reported regression of a canine fibrosarcoma and a feline squamous cell carcinoma following localized current field hyperthermic treatment at 43°C for 30 min and 700 rads given within 10 min after hyperthermia. The dog was treated a total of 7 times. There was no evidence of the fibrosarcoma 8 months after treatment. The cat was treated twice and had continuing regression 12 weeks after therapy.

Discussion

It has been suggested that in preparation for human clinical trials several animal tumor systems should be used to determine parameters for relevant endpoints, specifically tumor control and normal tissue complications (17). The advantages of spontaneous animal tumors in larger animals include the relatively large tumor volumes and correspondingly larger sizes of treatment fields. Longer follow-up times are also generally possible. Clinical data obtained through serial monitoring can be obtained in addition to the data of local tumor control and normal tissue response. Animals with spontaneous tumors often have concomitant diseases similar to those encountered in humans, which may or may not complicate the management of the tumor.

Investigators who have used spontaneous tumors in animals for evaluation of hyperthermia have been enthusiastic about them as experimental models. Marmor *et al.* (13) stated that the use of tumors in companion animals involves considerable added expense and requires cooperation of participating veterinarians. They felt, however, that the drawbacks might be overshadowed by the clinical relevance of the results obtained.

A program at Colorado State University over the past 5 years has shown that animal owners are willing to cooperate in humane experimental approaches to therapy often when only limited hope for cure can be offered. Although time and persistence are required, cooperation of referring veterinarians can be obtained. Follow-up has been consistent, and it has been possible to obtain necropsy information on approximately 85% of the animal tumor patients admitted to the Colorado State University Veterinary Teaching Hospital.

⁴ P. W. Day, personal communication.

The investigators who have studied the response of spontaneous tumors to hyperthermia have commented on the relative lack of normal tissue complications and have stated that repeat treatment could be done because of a lack of cumulative effects of hyperthermia (3, 13). The investigators have also implied that for effective control of tumors, irradiation combined with hyperthermia would probably be more effective. Crile (5) and Connor *et al.* (3) stated that one must be careful not to treat large tumor burdens too vigorously. Crile observed death of dogs in 8 to 18 hr following hyperthermic treatment of lymphomas, suggesting it was due to the results of sudden destruction of massive amounts of tumor tissue. Connor *et al.* (3) suggested that treatment of large tumor burdens might create a toxicity similar to the crushed limb syndrome. These types of observations are perhaps more easily made and investigated in larger animals than in rodent systems and point out the usefulness and the relevance of studies of response of tumors in companion animals.

Although the work with hyperthermia to date is limited to preliminary studies, it does cause regression of a variety of animal tumors. Unfortunately, little information is available about the dose response of the tumors treated with radiation alone. For an effective program of quantitative evaluation, it would be most useful to have dose-response assays for radiation alone and irradiation plus hyperthermia. Much valuable information can be obtained by comparing 2 protocols at one dose level; however, the studies would be of even greater value if dose response of tumors and of normal tissue complications could be plotted so the slopes of the response could be compared. Probabilities for increasing tumor control without significantly increasing normal tissue response can be estimated better from such curves.

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